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HUMAN BIOLOGY

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HUMAN BIOLOGY

BY

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PREFACE

"Human Biology" endeavors to present the pertinent facts of biology from the vantage ground of the most interesting and important organism in the world of life, namely, man. Accordingly, the study of human biology involves a great deal more than human anatomy and physiology; it is essentially a humanizing of general biology in that attention is centered primarily on human structure and function rather than on the characteristics of types selected from the lower organisms.

At least two major factors have influenced the author to devote the time and energy and to submit to the trials and tribulations necessarily associated with writing and publishing a college textbook in biology. First in importance has been the increasing realization, year by year, that the great majority of students beginning work in college biology were, inherently, far more interested in acquiring knowledge about the human organism than they were concerning any other living species. Student interest in any subject is naturally expected to lead to increased endeavor. Nevertheless, the author has frequently been surprised at the efforts voluntarily assumed by interested students in collecting the available information relevant to some structural or functional feature of man. Of first-rate importance in this connection is the fact that scientific data dealing with mammalian physiology and anatomy are available in abundance, possibly to a greater degree than elsewhere in the biological field. Furthermore, this body of scientific knowledge, particularly when associated with the functional aspects of man, is being augmented continuously from the results obtained by many investigators in the best laboratories of this and other countries.

Second, the author has been impressed with the necessity of supplying new and vital material at an advanced level for the basic courses in college biology. Biological knowledge possessed by the students now entering college is undoubtedly greatly superior both in quantity and quality to that of their predecessors. By this is meant that a larger percentage of students take a laboratory course in biology before entering college and that the material presented in these courses is much more extensive than in earlier years. Any college instructor

who takes the trouble to examine the contents of various excellent and widely used biology texts for secondary schools and representative student notebooks covering the year's work in these courses will certainly be convinced that careful consideration must be given to the content of college courses in biology so that the students' interest may not be dulled and their time wasted by the repetitious study of laboratory types which have been carefully considered in an earlier course. Particularly is this condition important to the great majority of college students electing biology, for their major scholastic interests lie elsewhere and they will, therefore, take only one year in the biological field.

The central problem is evident: Shall the incoming students be reintroduced at college levels to a series of more or less standardized biological types, most of which they feel—rightly or wrongly—are well known to them from previous study, or shall the college course be built, for the most part, around materials previously untouched? It seems evident that a biology course in which primary consideration is focused upon the organization and activities of human protoplasm offers new and superior possibilities for the presentation of highly important material and for increasing student interest in the biological field. If the human biology material is presented from a comparative standpoint, the student will learn not only the biology of man but also biology in its broader aspects, for man is a part of, not apart from, the world of life.

One example may be noted: The study of human nutrition cannot be completed until the photosynthetic processes of the green plants and the decay processes of the colorless plants are brought into the picture. The fact that the nutrition of every type of organism depends upon enzyme action gives opportunity for extended consideration of these organic catalysts which are involved in every vital process. And the same condition obtains with the other basic phenomena associated with the living state for, as is generally recognized, organisms perform the same vital functions in essentially the same way. They eat, grow, respire, secrete, excrete, react, and reproduce as a result of the activities of the associated cellular units of which they are composed. Accordingly, it seems evident that to "Know thyself" is not only an important and interesting discipline, but it may also be excellent biology.

In an endeavor to widen the scope of the book, so that the interested student may have abundant material to pursue important fields of interest at advanced levels, an Appendix has been supplied containing direct quotations from the publications of various authorities. It is

hoped that this material will prove to be highly stimulating to instructor and student and, at the same time, provide reference to a noteworthy list of books for additional collateral reading. Original material by the author has also been included in the Appendix when it was felt that its content tended to mar the continuity and appropriate level of the main text.

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May, 1940.

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John Wiley & Sons: "Animal Parasites and Human Disease," by Chandler; "Outlines of Biochemistry," by Gortner.

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HUMAN BIOLOGY

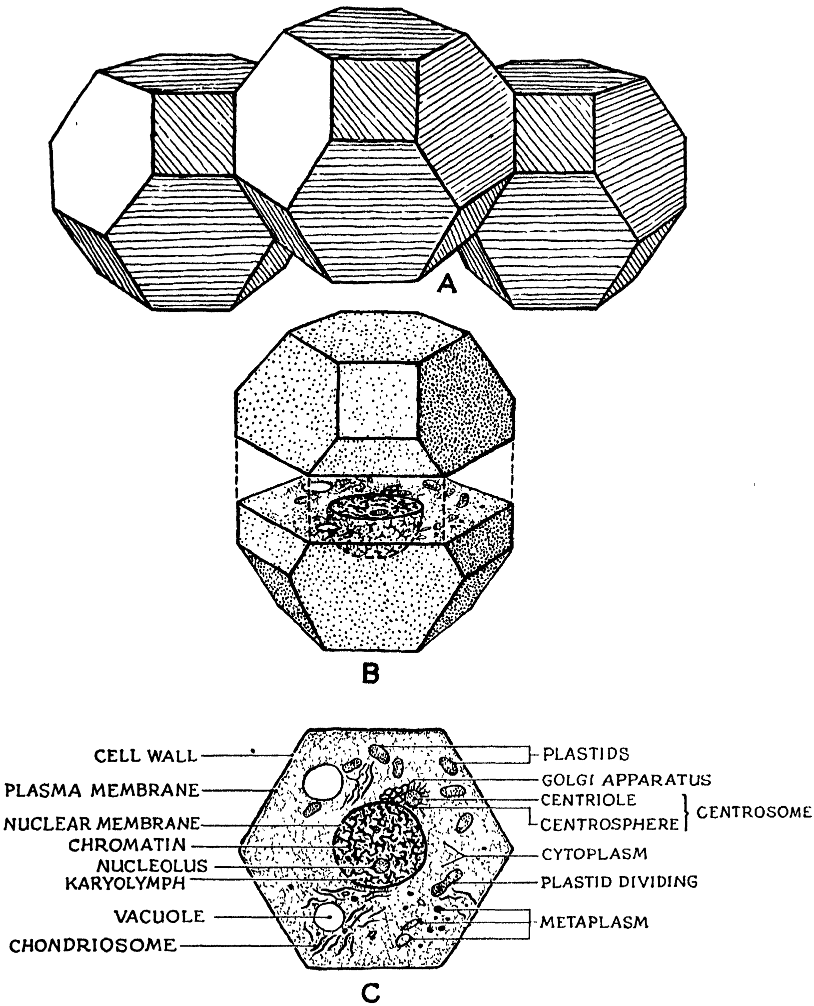


PLATE I.—Diagrams showing the cells as 14-sided figures (tetrakaidecahedra). *A*, three cells to show idealized arrangement in tissues of plants and animals as described by F. T. Lewis (*Proceedings of the American Academy of Arts and Sciences, vol.* 68, 1933); *B*, one of the cells sectioned to show internal structure; *C*, detailed study of section from *B* as observed in a microscopic preparation (*cf.* pages 20–23).

CHAPTER I

STRUCTURE AND FUNCTION IN THE WORLD OF LIFE

Biology is concerned with life phenomena of every kind and nature. Man recognizes life in the innumerable plant and animal organisms that are abundantly present in practically every niche of this earth, whether on land, sea, or air. And each of us, as a conscious human being, recognizes an inherent living principle that is linked with the surrounding world of life. Life is known to us only in the form of completely organized units which we term *individuals*. Also each individual in this world of life, whether small or large, simple or complex, plant or animal, is characterized by a number of fundamental structural and functional features that serve to distinguish it from nonliving organization and also to identify it as a distinct type of living organism. This unity of design and behavior, underlying all life, is due to the fact that the building material utilized in every type of living organism consists of a basic substance, technically designated as *protoplasm*, which is the vehicle for all life phenomena. Protoplasm, wherever found, exhibits certain unique structural and functional features that may now be indicated.

NATURE OF PROTOPLASM

Microscopic observations on protoplasm in living units show that it varies considerably in its physical state. It may appear at one time as a rather thick, slow-flowing liquid, such as might be described by the words "sirupy consistency" (the sol condition), and again as a more or less rigid, gelatinous substance (the gel condition). This variation in its physical state, together with other identifying characters, gives clear evidence that protoplasm is a colloid. The colloidal state is not a unique feature of living matter, for many nonliving colloids are known, both inorganic and organic. Colloids are characterized structurally by the presence of innumerable, exceedingly minute particles dispersed through a continuous medium. The dispersed materials are too small to be seen even under the highest magnifications. Colloids are heterogeneous, rather than homogeneous, systems. In the protoplasmic colloid the continuous medium is liquid,

but in other colloids it may be a solid or a gas, as in the case of a cloud, which is a colloid formed from a liquid and a gas, the latter serving as the continuous medium, with the minute water droplets dispersed

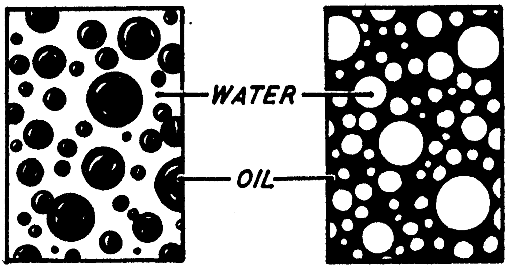


FIG. 1.—Diagrams illustrating the difference between cream (sol state) in which water is the continuous medium, with dispersed oil droplets; and butter (gel state) in which oil is the continuous medium. (*Buchanan, "Elements of Biology," Harper & Brothers.*)

throughout. Variation in the relations between the particles and the medium in which they are dispersed results in the reversible sol-gel states present in colloids. A common example of this phenomenon is found in the behavior of the fat globules in liquid cream, in which they are dispersed through a liquid medium. In butter, however, the

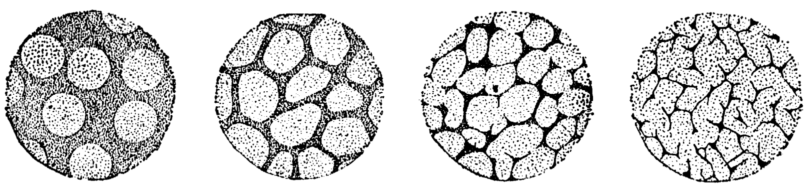


FIG. 2.—Diagrams showing variations in the microscopic structure of a colloidal emulsion. *A*, alveolar appearance when suspended droplets are widely separated by the continuous phase; *B* and *C*, reticular appearance present in continuous phase when droplets are close together; *D*, droplets now form the continuous phase following close apposition and coalescence. (*Sharp.*)

globules of fat are consolidated to form a continuous solid medium through which liquid particles are dispersed.[1] (Figs. 1, 2.)

From the functional standpoint, biologists are in general agreement that the colloidal state is essential to protoplasmic activity in that it permits the continuous energy transformations invariably associated

[1] Additional material on Colloids will be found in the Appendix. It will be found helpful to consult the Appendix frequently.

with every form of life. So long as there is life, there is activity. And activity, in this instance, does not mean simply movement but rather the continuous activity associated with the operation of the essential life functions, as will be discussed in the following chapters. Presumably, vital activities are dependent upon the fact that the protoplasmic colloid permits an unparalleled distribution of surface activity between dispersed particles and the medium, with the end result that potential molecular energy present in the nutritive materials is made available for maintaining the life processes. And, of course, it should be made clear that the energy thus released in the organism is the radiant energy of the sun previously stored in the foodstuffs by photosynthesis in green plants. The living organism can in no way manufacture energy; it can only indirectly utilize the radiant energy received from the sun for the maintenance of life activities.

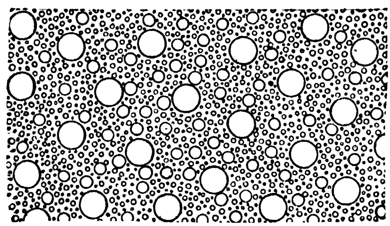


FIG. 3.—Diagram illustrating the microscopic appearance of an emulsion as often seen in protoplasm. (*Shull.*)

As might be expected from the structural variations occurring in protoplasm during life as the result of the reversible sol-gel phenomena, the appearance of the protoplasmic material is by no means uniform when it is preserved and prepared for intensive microscopic study by sectioning and staining. Accordingly, various concepts of the architecture of protoplasm are current in biological literature. As a matter of fact, one can speak only in very general terms on this subject, for our present knowledge concerning the ultimate structural organization of protoplasm is limited. This is due primarily to the fact that the basic organization pattern of protoplasm is so minute that it is ultramicroscopic—far beyond the highest magnifying powers of the microscope. Furthermore, scientific investigation along this line is definitely limited by the fact that protoplasm cannot be subjected to intensive analysis by any known method without destroying the primary object of the research, namely, the unique, dynamic life principle. The dead organic material, which was formerly living protoplasm, can, of course, be subjected to many intensive types of analysis, but such studies have so far failed to reveal the deeply hidden structural secrets that appear to be essential to the maintenance of life itself. (Figs. 3 to 5.)

Chemical analyses of protoplasmic material show that it contains a very high percentage of water, frequently more than 90 per cent by

weight, with various complex compounds in solution.[1] And so, according to one noted authority, the living organism is to be regarded

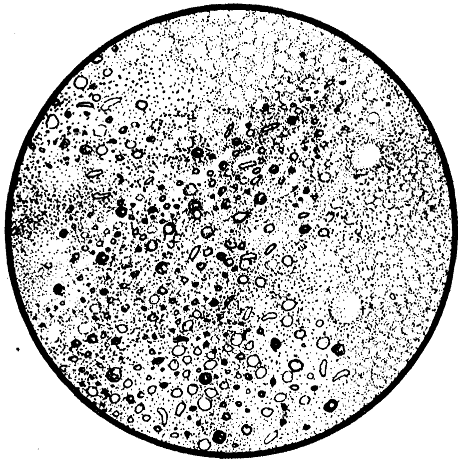


Fig. 4.—Living human protoplasm as it appears in a fresh, unstained preparation under high magnification. Specimen from epithelial cells in the lining of the mouth. (*Buchanan, "Elements of Biology," Harper & Brothers.*)

as "essentially an aqueous solution in which are spread out colloidal substances of great complexity." These complex constituent compounds present in protoplasm fall into three great groups of organic compounds designated as the *carbohydrates*, *fats*, and *proteins*. The first two of these contain only three elements, namely, carbon, hydrogen, and oxygen in widely varying proportions; but the proteins usually contain a wide range of common elements, in addition to the three just named. However, the chemical analyses show that, when the compounds present in protoplasm are broken down into their constituent elements, over 99 per cent of the material is derived from the following eight elements: carbon, oxygen, hydrogen, nitrogen, sulphur, calcium, phosphorus, and potassium. Also present are minute

Fig. 5.—Fibrillar structure of protoplasm as seen in a permanent preparation of a nerve cell. Highly magnified. (*Seifriz, after Tschernjachiwsky.*)

[1] Extreme limit in water content is apparently reached in the jellyfish, in certain species of which it is stated that the constituent tissues may contain as much as 96 per cent of water.

amounts of iron, chlorine, copper, sodium, magnesium, and probably many others. It is by no means certain, however, that all the elements present are actually bound up in the protoplasmic molecule.[1]

It is noteworthy that there is nothing rare or peculiar about these constituent elements which are present in protoplasm; they are of common occurrence. Gold, silver, platinum, and other rare elements are conspicuously absent. It is apparent, therefore, that the life qualities characteristic of protoplasm do not depend upon an assemblage of rare or unknown materials but rather on a unique and highly intricate arrangement of various common, widely distributed elements. Furthermore, it will be shown later that cycles of elements are present in nature, as the result of which the constituent materials pass repeatedly from the nonliving into the world of life and then back again to the lifeless state.

Cellular Organization.—Whatever may prove to be the ultimate arrangement of materials in the protoplasmic fabric, it is always revealed at the level of microscopic visibility in the form of definite entities, the cells; that is, a distinctive plan of organization pervades the life substance which is indicated by the term *cellular organization.* This means, in a word, that the common denominator of vital architecture is a tiny bit of protoplasm known to the biologist as the *cell.* Cells are protoplasmic building blocks which, associated in incredible numbers, constitute the basic materials, *tissues,* of plants and animals. In the primitive forms of plants and animals, many species are found in which the entire organism consists of a single microscopic cell, unassociated with other cellular units and completely equipped for maintaining all the life functions. These are known as the *unicellular organisms.* (Figs. 6–8; Plate II, page 18.)[2]

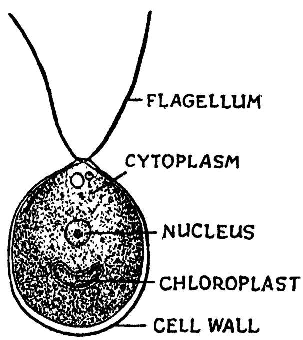


FIG. 6.—A primitive unicellular green plant, *Chlamydomonas.* Chlorophyll present in the crescent-shaped chloroplast. Highly magnified. (*Sinnott, after Goroschankin.*)

The bodies of higher organisms, including man and all the familiar forms of plants and animals, are multicellular. They are composed of an almost inconceivable number of cells. The examination of a bit of any plant or animal tissue under the microscope will quickly give

[1] Consult the section on Biological Elements in the Appendix for additional material.

[2] Consult the following sections in the Appendix for additional material: Protozoa, Amoeba, Paramecium.

visible evidence of the established fact that protoplasm does not occur as a homogeneous substance but rather as a mosaic composed of associated cellular units. And of even greater significance is the fact that each cell is an independent unit of life—a theater, as it were, in which the complete drama of essential life activities is continuously being enacted. For the functional activities inseparably associated with the living state are housed in the cells as the ultimate units of function as well as of structure. Someone has said that it is as if each of the tiny structural elements in a motor possessed a microscopic apparatus to duplicate the functions of the complete motor. (Fig. 10.)

PROTOPLASMIC ACTIVITIES

In the preceding pages it has been shown that a basic structural unity exists throughout the world of life. There is a common living

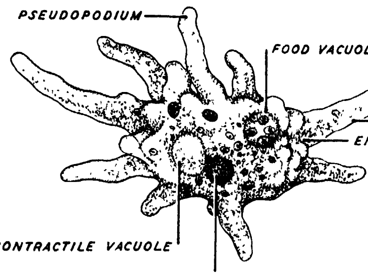


Fig. 7.—A primitive unicellular animal, *Amoeba*. Essentially a microscopic bit of naked protoplasm which flows in various directions to form temporary projections, pseudopodia. Highly magnified. (*Buchanan, "Elements of Biology," Harper & Brothers.*)

substrate, protoplasm, and a common design for building, cellular organization. But possibly even more impressive to the biologist is the functional unity that pervades—is essential to—all life, whether it be the most primitive form of microscopic plant or animal or man himself. That is to say, various essential life processes are continually in operation in the protoplasm of every living cell; and the organism as a whole is striving to provide the wherewithal, food, so that these vital activities may continue without cessation.

It is noteworthy that the principle that we call *life*, though extraordinarily abundant and operating in each one of us, is very difficult, if not impossible, to define. We conceive of life as a unique temporary state of matter, and there is nothing with which it can be compared. Accordingly, attempted definitions of life do not really define; they only describe certain outstanding characteristics. Thus it has been said that life is "the capacity of an animal or plant for self-preserva-

tion and growth, the cessation of which means death." Or again that it is "a series of definite and successive changes, both of structure and composition, which take place within an individual without destroying its identity." One of the most successful of the attempts to define life is that framed by the famous biologist and philosopher of the nineteenth century, Herbert Spencer, who defined life as "the continuous adjustment of internal relations to external relations."

Metabolism

This definition of Spencer's, it will be noted, stresses the dynamic or functional aspect of life with its continuous interplay between organism and environment, and truly this is a basic characteristic that immediately sets a living organism apart from the nonliving

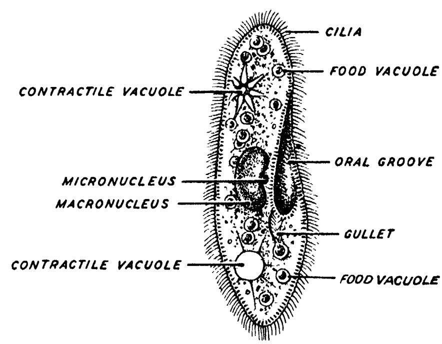


Fig. 8.—The highly specialized unicellular organism, *Paramecium*, as observed under the microscope. Some of the details are seen only in stained preparations. Note the even coat of cilia. Food vacuoles are moved through the cytoplasm by cyclosis. (*Buchanan, "Elements of Biology," Harper & Brothers.*)

world. For the living cells of all organisms continually admit essential materials from the environment and at the same time release substances that are no longer of value. A complex life chemistry is involved in these intracellular reactions—so complex in fact that, as yet, scarcely any of the processes are fully known. Certain basic facts relative to the chemistry of the life functions are, however, definitely established. Thus it is universally recognized that two essentially antagonistic processes are always involved, namely, a constructive, nutritive phase, *anabolism*, in which necessary materials are taken into the cell and assimilated and so made available for the protoplasmic repair, growth, and reproduction; secondly, a destructive phase, *katabolism*, which is marked by a disruption of the complex compounds, present in or forming a part of the life stuffs, with the constant release of energy for the maintenance of life functions. It is obvious that if the sum total of the anabolic processes exceeds that of the katabolic processes,

there will be a surplus, and an increase in the size of the cell or growth will result. The opposite of this condition, indicated by an excess of the katabolic reactions, must finally terminate in the death of the cell.

Anabolism and katabolism, together, include all the chemical activities essential to life and are usually grouped under the inclusive term *metabolism*. Metabolism means change and aptly describes the living state, with its continuous building up of the materials essential to growth and repair and its synchronous destruction of the energy-containing compounds in order that vital activities may be maintained. Yet through a lifetime of change, the protoplasm in each individual cell maintains an essentially uniform organization and exhibits a characteristic rhythmicity of function. Since the metabolic activities include all the chemical changes characteristic of life, they involve the essential life processes of nutrition, respiration, secretion, excretion, growth, reproduction, movement, and adaptation; all of which, in the final analysis, center in the cell as the basic structural and functional unit of life.

Energy Relations.—Intracellular chemical activities acquire their paramount importance from the fact that the maintenance of the essential life processes requires the continuous expenditure of energy.[1] This essential supply of energy is made available by oxidative processes, involving the assistance of enzymes or ferments, in the cytoplasm of each cell which result in the dissociation of various relatively unstable carbon compounds and the formation of simpler compounds of relatively low energy content which are given off from the cells as excretions. The oxidative phenomena essential to the release of energy require a continuous supply of free oxygen from the environment and the synchronous removal of the resulting carbon dioxide from the cells. This energy release and the associated interchange of oxygen and carbon dioxide constitute one of the most important of the metabolic processes, namely, respiration—a function that persists in every cell throughout life and is, at all times, a true measure of the extent of the life processes.

The destructive, energy-yielding, chemical activities in the cytoplasm are crudely comparable to the methods used to secure energy to run an automobile in which gasoline, a complex carbon compound with a high potential energy content, is vaporized and mixed with oxygen of the air. A very unstable mixture is thus obtained. An electric spark is used to upset the chemical equilibrium; oxidation of the gasoline occurs with explosive violence; and a considerable proportion of the stored potential energy of the gasoline is released as active,

[1] Consult the section on Energy in the Appendix for additional material.

or kinetic, energy in the cylinders. In part, this kinetic energy is utilized in the work performed in moving the car, and some is dissipated as heat. At the same time, various simpler and more stable compounds with reduced energy content, comparable to the cellular excretions, are formed which are released from the engine through the exhaust.

And so it is apparent that the living organism is not able to perform work without using energy any more than is a mechanical engine. The perpetual-motion machine, whether animate or inanimate, is a myth. All require suitable carbon compounds as fuel from which the potential energy can be released by oxidative processes. Both the steam engine and the gasoline motor are able to secure the energy from carbon-containing fuels which cannot be utilized in the living organism, but the principle is the same. It is important to note, however, that the living organism can do more than merely utilize foods for energy requirements. It can retain suitable portions for repair, for growth, and for reproduction—facilities entirely lacking in the mechanical engine.

Foodstuffs.—Three great classes of complex carbon compounds are available for use as food by man and other living organisms. These are carbohydrates, which include the various sugars and starches; fats, which include a wide variety of edible oils and fats; and proteins, which include an almost infinite variety of plant and animal tissues. The proteins are essential for cell nutrition because they always contain nitrogen and various other elements necessary to the repair and construction of protoplasm. The carbohydrates and fats contain only carbon, hydrogen, and oxygen and are utilized as a source of energy which may be used as needed to "keep the home fires burning," and the remainder stored away for supplying later requirements. Also the cells must be supplied with water, oxygen for respiration, various inorganic compounds, such as table salt, and minute but constant quantities of certain organic compounds, the vitamins, the exact chemical nature of most of which, as well as their functions in cell metabolism, is the subject of extended studies at the present time.

Photosynthesis.—The nutritive requirements just indicated are basically the same in both plant and animal cells; all are dependent upon the release and utilization of the potential energy stored in the foodstuffs. Inquiry as to the method of formation of suitable foodstuffs, essential to the maintenance of life, leads to a consideration of an all-important life function that occurs in green plant cells. This process, technically designated as *photosynthesis*, is superimposed upon the underlying metabolism of the plant cells and is based upon the

presence of a unique green pigment, chlorophyll, which originates in the cytoplasm of the plant cells. Chlorophyll makes it possible to utilize the radiant energy of sunlight for the formation, or synthesis, of complex carbon compounds suitable for food from the simple inorganic materials abundantly present in the immediate environment of the plant. Photosynthesis is fundamental for all life because, in the final analysis, it is the method by which the plant and animal foods are universally formed. Man and other animals get their food from plants, directly or indirectly. In the latter case, the carnivorous types utilize the tissues of plant-eating, or herbivorous, animals. Furthermore, and also of paramount importance, the photosynthetic processes of green plants release free oxygen into the air, which is essential to the animal respiratory processes by which the foods are utilized in the tissues of the body.

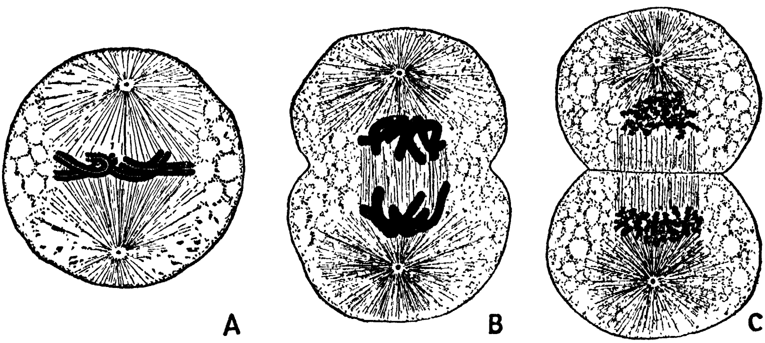
Cycle of Elements.—Not all plants are constructive food-forming types. There is an extremely abundant and diverse series of plant organisms, the so-called *colorless plants*, or *Fungi*, that are not equipped with the essential food-synthesizing chlorophyll of green plants and hence find it necessary to satisfy their nutritive requirements in essentially the same way as animals; that is, they require organic compounds of high complexity which trace their origin back to the photosynthetic processes. The fungi include such widely separated plant types as bacteria, yeasts, molds, mildews, mushrooms, smuts, and rusts. These include many species of parasitic organisms which attack the living tissues of man and his valuable plant and animal associates, thus producing a great many of our worst diseases. But of primary importance for our present consideration is the fact that the colorless plants are responsible for maintaining the cycle of elements in nature. They are really essential to the continued existence of life on this earth, for, through the various oxidative and decay processes incited by them and associated with supplying their own nutritive requirements, they release the essential elements and compounds locked in the tissues of dead plants and animals and in their wastes given off during life and thus make these materials once more available for photosynthetic food formation by the green plants. This, in essence, is the cycle of elements in nature which will be discussed in a later chapter.

Growth and Reproduction

When the food supply is plentiful enough for the living cells of any organism to secure the essential foodstuffs in such amounts that the continuous katabolic wastes are more than met, an increase in size, or growth, is possible. Growth in a living organism, often referred to as

intussusceptive, or *interstitial*, growth, depends upon the ability of the individual cells to secure and assimilate suitable materials from the environment, together with the transformation and intercalation of these substances into the protoplasmic complex. Thus, in the cells, additional *living* material is built from *nonliving* substances. This process of growth in the living organism is generally regarded as being of a different nature from that observed in the growth of crystals in saturated solutions. In the latter case, the increase of crystal size occurs through the external deposition of additional material secured from the surrounding saturated solution.

Cell Reproduction.—The size of all types of cell is quite definitely limited by inherent restrictive factors so that growth is brought to a



A B C

FIG. 9.—Cell division (mitosis) of the fertilized egg of the parasitic round worm, *Ascaris*, to form two daughter cells. The details of this process are considered in a later chapter. *A*, early stage (metaphase) with chromatin in center; *B*, separation of chromatin (anaphase) and, *C*, division between two daughter cells (telophase). × 1000. (*Haupt.*)

stop when a certain size has been attained. At this point, provided the dominance of the anabolic processes continues, another characteristic function of protoplasm appears, namely, reproduction, during which two daughter cells are formed by the splitting or division of the full-sized parent cell in half. Cell reproduction normally takes place following a complicated process known as *mitosis*, which involves profound nuclear changes. These result in the correct quantitative and qualitative division of the *chromatin* material in the nucleus of the dividing cell and its equal distribution to the two daughter cells. Since it is established that the chromatin is the chief vehicle for the transmission of hereditary characters, the necessity for an accurate division of the material is evident. Cell division is an exquisitely beautiful and exact process, the underlying mechanism of which has not as yet been fully revealed. On its normal functioning in every cell, during all the stages of embryonic development and throughout

life, depends the structural and functional integrity of every tissue and organ of the body and, in addition, the transfer of the specific characters to the next generation. (Fig. 9.)

Each of the two daughter cells, when first formed by cell division, is one-half the volume of the parent cell. Under normal conditions with suitable nutritive materials available, rapid growth occurs, and in a comparatively short time each of the half-sized daughter cells will have attained full size. And so we arrive at this fact, which is of the highest importance; namely, it is by repeated cycles of growth and cell division that man and all multicellular organisms gradually attain the adult condition. Each individual organism begins existence as a single cell, the fertilized egg, which is capable of continued growth and division into two, four, eight, and, finally, unknown millions and millions of associated and differentiated cells which constitute the complete organism. It is estimated that the cubic inch or so of living material present in the master tissue of all, the cortex of the human brain, contains more than nine billion cells. It is a staggering thought that all of these brain cells and the countless others present in the entire body of the human organism have arisen during development from the repeated division of a single microscopic cell, the fertilized egg, which is the basic life unit—the starting point of every living organism. (Fig. 13).

Irritability and Adaptation

Inasmuch as continuous metabolic activity is essential to the maintenance of life, it follows that the living organism must have at all times an environment that supplies the necessary materials and also provides suitable conditions of temperature and moisture. If a particular environment is too hot or too cold or too dry for a certain type of organism, metabolism may be hindered or entirely stopped. If water, oxygen, and the complex foodstuffs are not present in adequate supply, life cannot long persist. Of fundamental importance, therefore, since it is really responsible for all the life activities, is the omnipresent function of irritability which enables protoplasm to receive, interpret, and respond to stimuli from both its external and internal environment. Protoplasm is irritable, sensitive material and is therefore affected by the stimuli that impinge upon it. And, within certain limits, protoplasm can do something about the stimuli that are continually making themselves felt. Irritability results in adaptation that involves continuous temporary adjustments between the organism and its environment. If the organism finds that the environment is unsuitable, another is sought, or protective measures invoked if

possible; if it is hungry, it feeds; if more oxygen is needed, the intake is increased.

The environmental conditions are seen by the physiologist as definite fields of force resulting from the energy relations of the light, heat, temperature, electrical, chemical, and other phenomena that affect the organism. The oriented reactions of the organism in these fields of force are known as *tropistic reactions*, or *tropisms*. The response of the organism may be positive, negative, or neutral. Tropisms are very clearly in evidence in the lower types, such as the free-swimming protozoa. A broader phase of the adaptation problem is associated with the origin of the permanent adaptations that organisms exhibit on every hand. Thus fish are permanently adapted for an aquatic life and cannot secure the essential oxygen elsewhere, and the reverse condition is characteristic of the air-breathing types. Temporary adjustments cannot be made to overcome this permanent "built-in" adaptation to a particular environment.

Adaptation is seen, therefore, to be dependent upon the fact that protoplasm possesses a certain degree of plasticity; it can make adjustments to environmental changes that do not transgress the outer limits. Everything in life involves the function of irritability and the adaptive response. Furthermore, the latter does not appear to be haphazard in the higher types possessing a nervous system. There is coordinated control of the complete organism, extending down to cellular levels. Coordination is of supreme necessity in unifying the activities of all the structures responsible for the essential life functions and, through the amazing development of the central nervous system, leads to the very pinnacle of life phenomena in the human mental processes.

Movement

Even a superficial examination of the various activities associated with protoplasm, as indicated in the preceding pages, shows that the function of movement is inseparably bound up with most of them. In fact, visible spontaneous movement is one of the most characteristic and readily recognizable activities associated with the living state, particularly in the higher animal types. The microscopic study of living cells, both plant and animal, gives additional evidence of the universality of protoplasmic movement in revealing a regular intracellular flow, or streaming, of the cytoplasm, which is undoubtedly tied up with the maintenance of the other life processes. This is the phenomenon of cyclosis which, in a favorable type of cell such as the unicellular Paramecium, is seen to be essential both for the distribu-

tion of nutritive materials and for the elimination of waste substances. (Fig. 8.)

In addition to the intracellular cyclosis, Paramecium and many other unicellular organisms have filaments of cytoplasm projecting through the cell boundary into the surrounding medium. Through a beautifully coordinated oar-like beating movement of these cilia, the ciliated animal is able to move about in search of food or of more favorable environmental conditions. And cells, with essentially the same type of ciliary action, line various ducts and cavities of the higher organisms and serve to move various materials. The need for a motor tissue to supply the host of movements required in the multicellular animals for locomotion and other activities has been met by the development of the contractile muscle tissue, which is one of the most highly developed of all the tissues and also one of the most widely distributed. If the muscle tissue of a vertebrate were removed, together with the accessory bones, tendons, and nerve tissue, all of the organ systems would be dismantled, and only a relatively small amount of unorganized cellular material would remain. Coordinated muscular movement is essential throughout the vertebrate organism. (Figs. 10, 17, 21.)

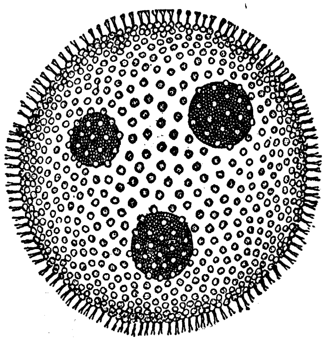


FIG. 10.—The primitive multicellular organism, *Volvox*. Barely visible to the naked eye as a spherical colony. Microscopic examination shows that the colony consists of several thousand chlorophyll-bearing cells, each with two flagella. Asexual reproduction by daughter-colonies (three are shown); sexual reproduction by eggs and sperm (not shown). (*Sinnott, after Cohn.*)

And so biologists find in protoplasm a unique material of the highest complexity which exhibits, in man and all organisms, various definite characteristics in its structural organization and also in the associated functional features, which may be summarized as follows: All the vital processes center in the cell as the fundamental unit of structure and function, and all are bound up with the fact that the living state requires the constant expenditure of energy to keep it going. The energy for all types of life is originally received from the sun by means of the photosynthetic activity of the green plants and then stored as potential chemical energy in complex carbon compounds. The latter also contain the elements necessary for the repair and growth that involve the construction of new protoplasm. There is a cycle of elements in nature by which the materials used in the living

organism are returned to the inorganic world and thus made available once more for food formation.

In the following chapters an endeavor will be made to show how the basic biological features, just noted, which pervade all types of life, are exhibited in the human organism. Thus it is hoped that a clear conception may be gained of the materials and methods used by Man—a dominant and highly developed type of life—in the solution of the fundamental problems associated with the maintenance of the living state and the propagation of his kind.

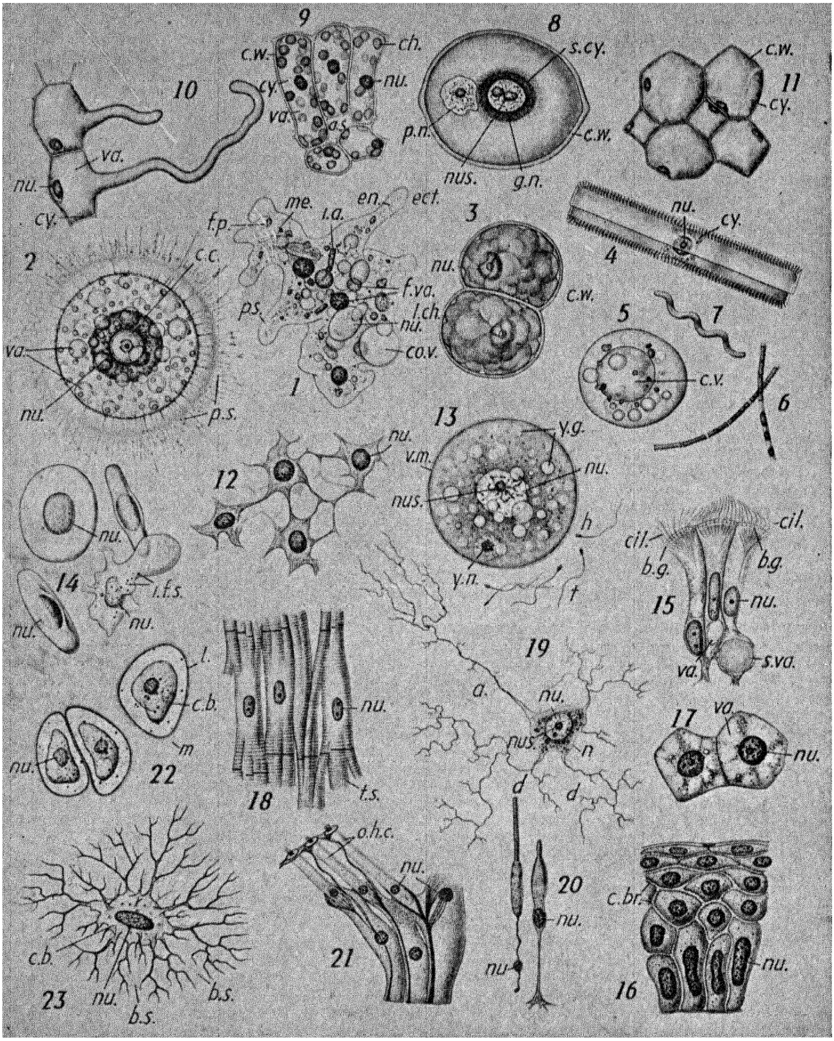


PLATE II.—Cell types. Drawings of a considerable variety of plant and animal cells from microscopic observations, as follows: 1, Amoeba, a primitive unicellular animal; 2, Radiolaria (*Thalassicolla*), a relative of Amoeba; 3, Protococcus (2 cells), a primitive plant cell; 4, Diatom (*Pinnularia*), a unicellular marine plant; 5, yeast plant; 6, Anthrax bacillus; 7, Spirilla, a type of bacteria cell; 8, pollen of lily; 9, cells from leaf (*Castania*), with chlorophyll; 10, root-hair cells from corn root; 11, pith cells from corn stem; 12, embryonic tissue of chick (mesenchyme); 13, egg and sperm of cat (sperm proportions large); 14, blood of frog, showing three red blood corpuscles (erythrocytes) and one amoeboid blood corpuscle (leucocyte); 15, ciliated epithelium from intestine of clam; 16, stratified epithelium from skin of frog; 17, liver cells of cow during digestion; 18, cardiac muscle fibers; 19, nerve cell from rabbit; 20, visual cells from human retina (rod and cone); 21, auditory cells from organ of Corti (guinea pig); 22, cartilage cells from frog; 23, bone cell. ***Abbreviations:*** *a.*, axon; *a.s.*, air space; *b.g.*, basal granules; *b.s.*, bone substance; *ca.*, canaliculi; *c.b.*, cell body; *c.br.*, cell-bridge; *c.c.*, central capsule; *ch.*, chloroplast; *co.v.*, contractile vacuole; *c.v.*, central vacuole; *c.w.*, cell-wall; *cy.*, cytoplasm; *d.*, dendrites; *e.c.*, epidermal cells; *ect.*, ectoplasm; *en.*, endoplasm; *f.p.*, food particle; *f.v.*, food vacuole; *g.n.*, generative nucleus; *h.*, head of sperm; *i.a.*, ingested algae; *i.f.s.*, ingested foreign substance; *l.*, lacuna; *l.ch.*, lobed chloroplast; *m.*, matrix; *me.*, metaplasm; *n.*, neuron; *nu.*, nucleus; *nus.*, nucleolus; *p.n.*, pollen-tube nucleus; *ps.*, pseudopodium; *r.h.*, root-hair; *s.*, spore; *s.v.*, secretory vacuole; *s.cy.*, specialized cytoplasm; *t.*, tail of sperm; *t.s.*, transverse striation; *va.*, vacuole; *v.m.*, vitelline membrane; *y.g.*, yolk globule; *y.n.*, yolk nucleus. ***Drawn by J. M. Valentine, Ph.D., for Weber's Biological Chart "Cell-Types," New York Scientific Supply Co., New York.)***

CHAPTER II

THE ORGANIZATION OF THE HUMAN BODY

The human body exhibits the characteristic cellular organization that is everywhere apparent in the living world. Examined microscopically, bits of the various body materials, such as brain, bone, muscle, liver, or skin, reveal the presence of the constituent cells. The number of these microscopic life units in even a small amount of tissue reaches almost incredible figures. It has been estimated that in the body of the child at birth there are approximately 26 trillion cells, with a total weight 1,500 million times that of the original egg cell. Both the number of constituent cells and the weight are still further increased before maturity is reached. All these cells are derived by the repeated splitting of a single cell, the fertilized egg, which marks the starting point of each individual life. When one considers the number of cellular divisions, beginning with the fertilized egg, that are essential to produce the 26 trillion cells of the body, the number does not seem so difficult of attainment; for if a cell divides forty-six times, and each of the resulting cells continues to divide regularly after each division, the number, represented by 2^{45}, would be reached. (Fig. 13.)

A survey of the world of life shows that in the more primitive multicellular plants and animals many examples can be found of colony formation in which, as the name suggests, the organism consists of a number of associated cells, all of the same design and with each cell functioning as an independent unit. In the higher multicellular types of life, a dependent type of cell association is found in which the activities of the individual cells are much more restricted than in a colony. This restriction is due to the fact that cellular differentiation has entered into the picture and become of great importance. Cellular differentiation in an organism means that groups of cells are structurally modified to perform some function essential to the organism as a whole, such as digestion, respiration, or movement. Thus there is a segregation of function, a *division of labor*, between the various groups of differentiated cells. For instance, certain cells lining portions of the alimentary canal are responsible for the digestion and absorption of food, and they are structurally differentiated for these functions. Such nutritive cells would not find it possible to function in vision.

nor would the visual cells of the eye be of any use in the alimentary canal. Each cellular type is a specialist in its field. And so it is clear that structural differentiation among groups of cells leads to functional division of labor in which certain cells perform specific functions for the organism as a whole and, in return, are cosharers in the benefits derived from the activities of the other specialized cellular groups. It is to be remembered, however, that every cell, no matter how highly differentiated it may be for its particular service to the organism, must be able to maintain the independent intracellular life functions essential to its own existence. (Figs. 10, 11.)

Cellular differentiation is responsible for the construction of special building materials, the tissues, as seen in nerve tissue, skin tissue, or

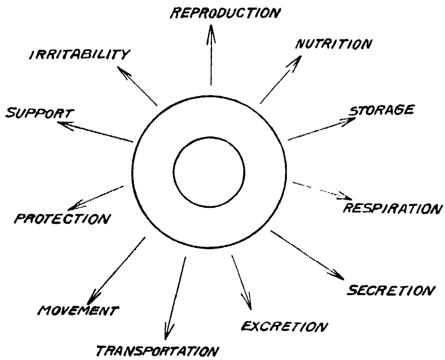


FIG. 11.—Diagram showing the possibilities of cellular differentiation inherent in the fertilized egg cell of a higher organism. (*After Rogers; slightly modified.*)

muscle tissue. Thus the metazoan body is composed of distinct kinds of living tissue which have characteristic structural and functional features. The cells of muscle tissue, the cells of nerve tissue, the cells of the blood, and various other kinds, though basically related in that they are all descendants of the fertilized egg, show marked diversity in their characteristic features. Furthermore, the tissues are not the final stage of organization in living architecture, for they are combined into larger structural and functional units, the organs, as shown, for example, in the heart, liver, or brain. And, finally, the organs concerned with a particular function are associated into the major organ systems that together make up the complete functional organism. Consideration may now be given to the structural features of cells. (Fig. 12.)

CELL STRUCTURE

A typical cell consists of a microscopic globule of protoplasm differentiated into *cytoplasm,* which forms the main mass of the cell body,

and a very much smaller spherical body, the *nucleus*, usually situated near the center of the cytoplasm. The cytoplasm is always enclosed by some type of a limiting membrane that forms the cell boundary. Cells are known, for example, in the primitive unicellular animal Amoeba, in which this limiting membrane consists merely of a slightly modified region of the peripheral cytoplasm, the plasma membrane. Usually, however, in addition to the plasma membrane, an outer cell wall of varying thickness is present, formed as a nonliving secretion by the peripheral cytoplasm, so that the cell is doubly enclosed. In any case, the limiting membranes of all cells are of such a nature as to permit a continuous interchange of materials between the living cell and its environment, which is essential to life.

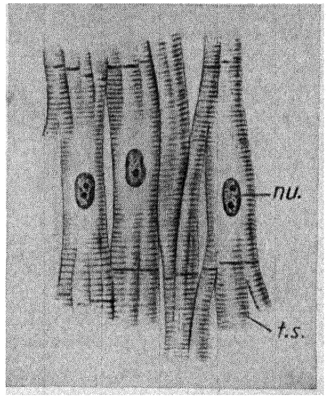


FIG. 12.—Muscle fibers from the cardiac tissue of the vertebrate heart. Highly magnified. *nu.*, nucleus; *t.s.*, transverse striations. (*Weber, Valentine.*)

Cells present a galaxy of shapes in the infinite variety of living forms in the plant and animal kingdoms. Almost every conceivable shape can be found, ranging from spherical egg cells to free-swimming male gametes. Possibly we are inclined to regard the egg cells as typical in shape, but it might be questioned if they are any more

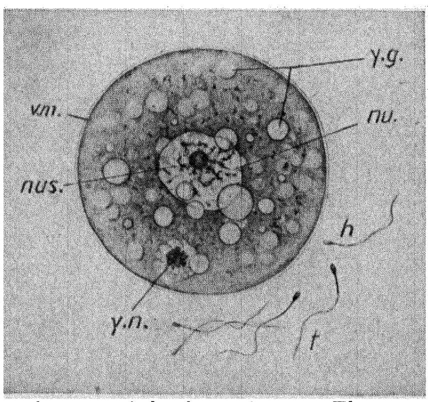


FIG. 13.—Egg cell and sperm of the domestic cat. The sperm are magnified more highly. *h.*, head of sperm; *nu.*, nucleus; *nus.*, nucleolus; *t.*, tail of sperm; *v.m.*, vitelline membrane; *y.g.*, yolk granules; *y.n.*, yolk nucleus. (*Weber, Valentine.*)

typical than the active sperm that fertilizes them (Fig. 13). However, recent researches show that the cells present in the tissues of plants and animals are typically 14-sided figures (tetrakaidecahedra). It has

also been shown, in some instances, that the embryonic cell is an eight-sided figure, that is, one with six sides plus the top and bottom. The mature 14-sided cell body is attained from the eight-sided cell as a result of the pressure of adjacent cells that divides each of the six sides into two parts, thus giving cells with 12 sides, in addition to the top and bottom, to make a total of 14 sides. (Plate I, page 2; Fig. 14.)

Cytoplasm.—The cytoplasm contains a number of differentiated bodies of distinctive design and function, notably plastids, chondriosomes, and Golgi bodies, all of which undoubtedly have essential assignments associated with the life functions of the cells. Almost all of these tiny units present in the cytoplasm are still the subjects of extended research in an endeavor to find the answers to the numerous problems involved in cell function. The plastids are of particular interest to the biologist because of the fact that a certain type of plastid, the chloroplast, found in the green plant cells, contains the basic food-forming substance, chlorophyll, which, as shown above, is really responsible for the formation of all plant and animal food. Another tiny body, the centrosome, which is very active during cell division or reproduction, is a characteristic feature of animal cells. It lies in the cytoplasm close to the nuclear wall.

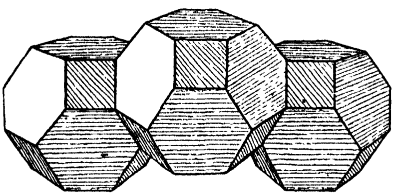


Fig. 14.—Idealized arrangement of 14-sided cells (tetrakaidecahedra) in tissues. (*After F. T. Lewis.*)

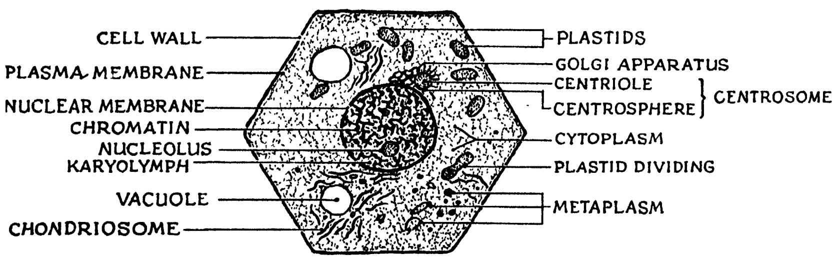


Fig. 15.—Diagram illustrating the cytoplasmic and nuclear elements of a cell as described on pages 22–23. Highly magnified. *Cf.* also Plate II.

In addition to the various cytoplasmic inclusions, as just noted, a more or less heterogeneous assemblage of nonliving materials, commonly referred to as metaplasm, are present. The metaplasm varies greatly in character and amount in different types of cell and in the same cell at different times. It consists chiefly of waste products and reserve food materials and may be in the form of fat droplets, crystals, water, cell sap, etc. The liquids are typically present in tiny cavities

or vacuoles. Mature plant cells, particularly, often possess a large central cavity, the cell vacuole, which is filled with the cell sap containing materials essential to the nutrition of the cell. (Fig. 15.)

Nucleus.—Of paramount importance in the cell is the nucleus. This minute intracellular body is generally regarded as the main directing agency of the cell and also as the portion primarily responsible for the control of inheritance. The nucleus, surrounded by a special nuclear membrane, consists of highly differentiated protoplasm, in which, in properly prepared material, a delicate fibrillar network, the reticulum, appears to permeate a homogeneous fluid ground substance, the karyolymph. The most important feature of the nuclear protoplasm is, however, the chromatin present in the reticulum;[1] the chromatin derives its name from the fact that, during mitosis, it stains heavily with certain dyes used by histologists in preparing microscopic preparations.[2] It is known to be the chief vehicle for the transmission of hereditary characters from one generation to the next, and, with such a major assignment in the economy of life, its dominating position is evident. The complicated methods of cell division, or mitosis, involved in carrying out this transmission will be considered in the later chapters on Reproduction and Heredity. It may be said that the appearance of chromatin varies in accordance with the cellular condition. In a resting cell, it is more or less granular; whereas in a cell preparing to divide, the chromatin condenses to form a definite number of chromosomes, which are of characteristic size and shape in a particular species and readily studied when properly stained. Also frequently present in the nucleus is a minute spherical nucleolus, the function of which is quite obscure. (Figs. 9, 15.)

HUMAN TISSUES

Man as a representative vertebrate is a very highly specialized organism with a wide variety of body tissues, which arise comparatively early in development as the cells become differentiated. Differentiation is a gradual process and begins essentially with the formation in the early embryo of three primary tissues, ectoderm, mesoderm, and endoderm, which together are known as the *primary germ layers*. Later specialization among the cells of the three germ layers results in the development of the diversified tissues present in the adult body. The study of the vertebrate organism reveals the presence of five basic types of tissue which are almost omnipresent throughout the body structures. Each of these, as will be seen later, is variously

[1] Reticulum is also designated as *linin*.

[2] Consult the section on Histology in the Appendix for additional material.

subdivided into more specialized tissue types. The constituent tissues are (1) epithelial tissue, which forms a covering material over the exposed surfaces of all organs, whether internal or external, and also functions in various other ways as noted just below; (2) connective tissue, which forms the framework of the body and each of its parts, giving support and protection to the delicate cells and tissues and forming the levers by means of which many of the muscular movements are translated into action; (3) vascular tissue, which is responsible for the transportation of a host of essential materials to all the cells of the body and also for carrying the cellular wastes to the excretory organs; (4) muscle tissue, which is specialized for contraction and responsible for the continuous and almost innumerable movements associated with the functioning of the typical animal; and, finally, (5) nerve tissue, which is the supreme coordinating and directing agency of the body and, with its associated sensory tissues and conducting paths, constitutes a tissue system of the greatest complexity and supreme importance. With reference to their origin, it is found that the muscular and vascular tissues are definitely mesodermal, that nerve tissue is ectodermal, whereas all three germ layers make their contribution to the epithelial and connective tissues. Mention should also be made of (6) the germinal tissue, which is localized in the gonads and serves primarily for the propagation of the species rather than for the needs of the individual.

Brief consideration may now be given to the fundamental structural and functional features of the five body tissues that are intimately associated in the various organs and organ systems to make the complete functioning organism. In the later chapters dealing with the various organ systems, additional consideration is given to each of these tissues and associated organs.

Epithelial Tissue

A considerable variety of epithelial tissues covers the numerous exposed body surfaces, both internal and external, as well as the linings of cavities and ducts. Thus the outer tissue of the skin or epidermis, which is in constant contact with the external environment, consists of several layers of epithelial cells. The cells are considerably modified according to their position. The outermost layers are built up of exceedingly thin, flattened cells, lying in close contact to form a tile-like surtace, the so-called *squamous epithelium*. Next in order, below, are thicker cells, the shape of which is well described by the term *cuboidal epithelium*. Finally, there is a *columnar epithelium*, in which the cells are found to be elongated, more or less tubular units.

The type of epithelium just described, which consists of a number of cellular layers with a gradual change in shape, is commonly termed *stratified epithelium* and may be found covering various body structures. Other important covering types of epithelium are found in the

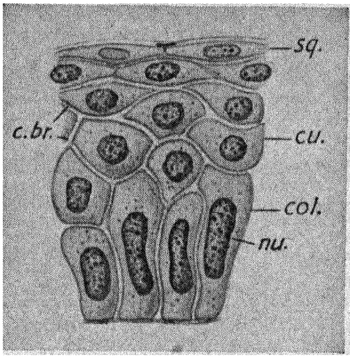


FIG. 16.—Stratified epithelium from the skin of the frog. *c.br.*, cell bridges; *col.*, columnar cells; *cu.*, cuboidal cells; *sq.*, squamous cells of outer surface. (*Weber, Valentine.*)

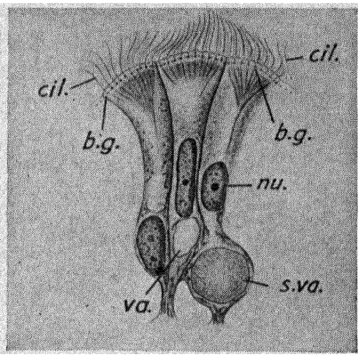


FIG. 17.—Ciliated epithelial cells from the intestinal lining of a clam. *b.g.*, basal granules; *cil.*, cilia; *nu.*, nucleus; *s.va.*, secretory vacuole; *va.*, cell vacuole. Highly magnified. (*Weber, Valentine.*)

peritoneal epithelium lining the abdominal cavity and in the epithelium of the alimentary canal which covers it inside and out. The epithelium lining the alimentary canal, endodermal in origin, is of particular importance because it consists of the nutritive cells of the body which are essential to the digestion and absorption of the foodstuffs. (Fig. 16.)

The cells of another important type of epithelium bear cilia on the exposed surfaces and accordingly give rise to ciliated epithelium. This type of epithelial tissue is found in the lining of various ducts and tubular structures in the body where movement of the enclosed liquids and other substances is required. This is accomplished by the coordinated action of the beating cilia. Examples of ciliated epithelium may be found in the lining of the nasal and throat cavities, in the oviducts, and in ducts of the kidneys. (Fig. 17.)

Many types of gland, which manufacture and secrete important substances, are developed from specialized epithelial cells and so give rise to glandular epithelium. Such glands may be unicellular glands or goblet cells, each of which is formed from a single secreting cell, as found in the epithelium lining various regions of the alimentary canal (page 52). It will be found, however, that most of the glands present in the body are multicellular. Common examples of these are seen in the sweat glands of the skin and also in the sebaceous glands

of the hair, which secrete an oily substance. Noteworthy are the paired mammary glands of the mammalian female, which secrete an abundant supply of milk to nourish the newly born offspring. In certain domesticated animals, notably the goat and cow, the mammary glands are particularly well developed, and the milk that they synthesize is highly desirable for human consumption. (Fig. 18.)

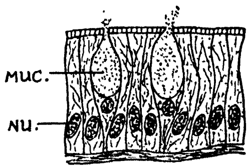


FIG. 18.—Glandular epithelium. Two goblet cells are shown from the nutritive epithelium of a vertebrate, with the extrusion of the mucous secretion. Highly magnified. *muc.*, mucus in glandular portion of goblet cell; *nu.*, nucleus of typical epithelial cell. (*Wolcott.*)

Finally, the surface epithelial cells of the body are, in numerous instances, modified to form peripheral sense organs, which function in association with the nervous system. Such epithelial cells form a very important type of ectodermal epithelium, the sensory or nervous epithelium, examples of which are to be found widely distributed in the epidermis of the skin, where they respond to cold, heat, pressure, etc. The sense of taste and the amazingly keen olfactory sense are also due to the activities of sensory epithelial cells.

CONNECTIVE AND SUPPORTING TISSUES

Multicellular animals require a considerable variety of connective and supporting tissues, widely distributed throughout every region of the body, for the support and protection of the various organs. These tissues are commonly divided into the exoskeletal and the endoskeletal types and attain their highest development in the vertebrate animals.

The outer, or exoskeletal, tissues form a more or less complete protective covering over the underlying soft tissues. In the vertebrates, the exoskeleton develops primarily by the transformation of skin tissues. In certain vertebrates such as the turtle, the exoskeleton forms a protective covering over practically the entire body. In the majority of vertebrates, however, the exoskeletal structures, represented by hair, feathers, nails, claws, or scales, are more or less restricted in their coverage and may even be entirely lacking, as in the frog.

The endoskeletal structures are internal, comprising many types adapted to widely varying needs and culminating in bone tissue, which is regarded as the highest development of the endoskeleton. In general, the endoskeletal tissues contain a relatively large amount of collagenous ground substance, or matrix, which is intercellular in position; that is, it lies between the cells, not enclosed by the cell walls In some of the connective tissues, the ground substance constitutes by

far the larger amount of material. It begins to develop very early in the embryo as a secreted, nonliving substance which in time becomes variously modified as may be required for a particular type of tissue. For example, the ground substance may remain largely unchanged, as in some of the less differentiated types of connective tissue; it may become transformed into a dense fibrillar material, as in the tendons that connect muscles with bones; or it may become heavily infiltrated with inorganic lime salts, chiefly calcium carbonate, and form the main substance of the hard bone tissues. (Fig. 19.)

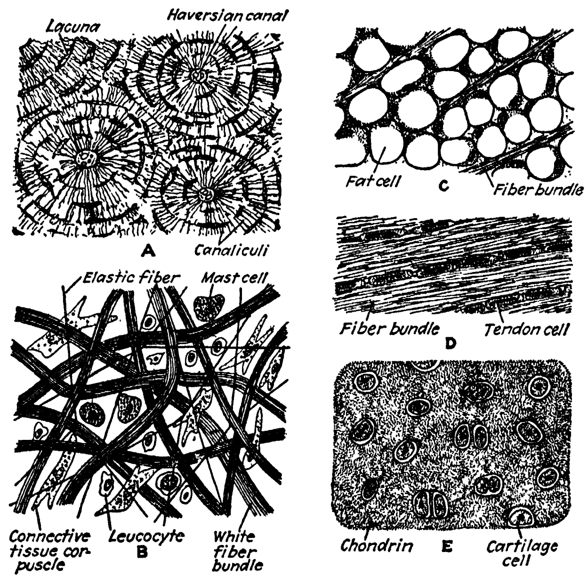


FIG. 19.—Various types of vertebrate connective and supporting tissues; somewhat diagrammatic. *A*, bone; *B*, white fibrous tissue; *C*, fatty (adipose) tissue; *D*, tendon largely composed of bundles of white fibers; *E*, cartilage. Highly magnified. (*Wolcott.*)

Five basic types of endoskeletal tissue are usually recognized by the histologists. The essential features of each may be briefly indicated at this time and then left for further consideration in the later chapter on the Skeletal System.

White fibrous tissue is widely distributed throughout the vertebrate body and accordingly may be obtained from almost any region as, for example, in the skin, permeating and surrounding the muscles, nerves, and various organs of the body. Tendons, which connect muscles with bones, are almost entirely white fibrous tissue. (Fig. 19*B*.)

Elastic tissue is found chiefly in the walls of the blood vessels but also in various other places where give and take is essential, notably in the ligaments, which are highly elastic. Elastic tissue is constructed

in such a way that it will stretch and then return to the original condition when the tension is released. This is the reverse condition from that found in the white fibrous tendons, which lack elasticity and therefore transmit the full strength of the muscle contraction to the attached bones. (Fig. 19*B*, *D*.)

Fatty, or adipose, tissue is generally regarded as a modified type of fibrous tissue in which the cells have become enlarged and adapted for the storage of fat resulting from an excess of nutritive materials. It is rather widely distributed throughout the body. (Fig. 19*C*.)

Cartilage is a highly developed connective tissue which is particularly abundant in the vertebrate embryo. In the lower types of vertebrates, cartilage remains throughout life as a permanent skeletal framework, but, in the higher types, it is largely replaced by bone tissue. Even in the highest animals, various cartilaginous areas remain unchanged, as in the joints, between the separate vertebrae of the backbone, in the nose, and in the outer ear. Cartilage is characterized by the presence of an exceptionally large amount of a transparent collagenous ground substance possessing considerable elasticity and great strength. (Fig. 19*E*.)

Bone, for the most part, is first laid down in the embryo as cartilage. Such bones are known as cartilage bones in contradistinction to the much less common membrane bones in which the bone tissue is formed by the gradual ossification of soft fibrous tissue membranes rather than by the cartilage transformation. The general structure of bone is highly intricate, with the ossified matrix arranged in concentric layers and containing numerous widely branching cavities in which the bone cells lie. It is covered on the outside by a soft connective tissue sheath, the periosteum, which is continuous with the tendons. Bones typically contain a central cavity filled with a soft, highly vascularized tissue, the bone marrow, which has a very important function in association with the vascular system in blood cell formation. The human bony skeleton comprises some 200 separate bones and is of major importance in various functional activities of the organism. (Fig. 19*A*.)

Vascular Tissue

Permeating every nook and cranny of the human body is the vascular tissue which functions as a continuous transportation system. Vascular tissue does not occur in the relatively simple animals with a tiny body and low degree of tissue differentiation. It is first present in what we may term the "earthworm stage of development" and is of increasing prominence throughout the vertebrate series, where it

constitutes one of the most complex and prominent of all the organ systems. Vascular tissue may possibly best be thought of as consisting of (1) a specialized type of epithelium, the endothelium, which lines every type of blood vessel throughout the organism; and (2) a liquid tissue, the blood, the only example to be found in the body in which the intercellular ground substance is fluid in nature and permits the blood cells to float freely in it.

The liquid portion of the blood, the plasma, is not regarded as living material. It is colloidal in nature and a very heterogeneous mixture—a temporary storehouse, as it were, for the multitudinous nutritive requirements of all the body cells and for their secretions and excretions as well. Under the proper conditions, the blood plasma clots to form a permanent gel; the latter is essential in the stoppage of blood flow, as in an injury. Blood coagulation is also probably linked up with the formation of the connective tissue ground substance. In fact, vascular tissue is commonly regarded as one of the various types of connective tissues.

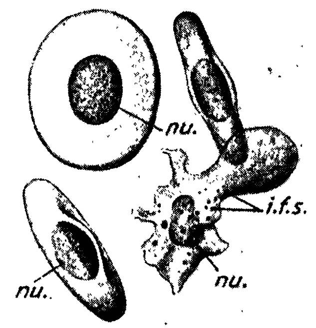


FIG. 20.—Blood cells of the frog: three nucleated red blood corpuscles (erythrocytes) and one amoeboid white cell (leucocyte). Highly magnified. *i.f.s.*, ingested foreign substances; *nu.*, nucleus. (*Weber, Valentine.*)

The living cellular elements of the vascular tissue consist of the blood cells circulating in the plasma and the endothelial cells lining the blood vessels. The latter are believed to function in the formation and secretion of the blood plasma and also, to some extent, in the formation of the specialized blood cells. To the formation of the latter, the bone marrow and spleen tissue also make important contributions. The complete picture of the functional and structural attributes of the blood may be deferred for later consideration as an organ system. (Fig. 20.)

Muscle Tissue

Muscle tissue, since it is the source of power for all bodily movements, is necessarily very widely distributed throughout the body. It may be divided into three distinct types: smooth, striated, and cardiac. Of these, only the striated muscle tissue is voluntary, that is, under the direct control of the will. The smooth muscle tissue is under the involuntary control of the autonomic nervous system, whereas the

cardiac type, found only in the heart, possesses an inherent power of rhythmic contraction which, however, is subject to general regulation by nerve impulses. (Figs. 12, 21.)

The smooth, or involuntary, muscle tissue is regarded as the simplest type structurally. It is widely distributed, forming the muscular layers in the walls of a number of important organs, such as those of the alimentary canal, blood vessels, and urinary bladder. A microscopic examination shows that it consists of long pointed cells, each with a prominent nucleus elongated in the same direction as the cell body. The cells are frequently branched at the ends. Also their length varies considerably. For example, in the walls of the blood vessels they are typically short and thick, whereas in the walls of the bladder they tend to be long and thin. The cytoplasm shows a fine, longitudinal striation which is very different from the marked transverse striation characteristic of the striated muscle tissue. The smooth muscle cells lie close together and are essentially embedded in an intercellular matrix of connective tissue elements. So they are closely held together and work as a unit in the muscular contraction. The rate of contraction of smooth muscle is much slower than that of striated muscle tissue, but the movements can be continued almost indefinitely without tiring. (Fig. 21*B*.)

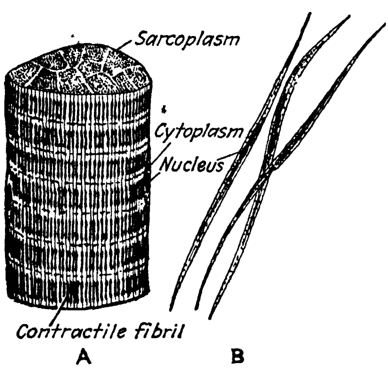


FIG. 21.—Vertebrate muscle tissue. *A*, portion of striated muscle fiber; *B*, three isolated cells of smooth muscle tissue. Highly magnified. (*Wolcott.*)

Striated, or voluntary, muscle tissue is largely localized in the muscles of the body wall and those of the arms and legs, where we find it divided into definite contractile units, the muscles proper. Altogether, there are some 374 voluntary muscles in the body. Muscle contraction is translated into bodily movement through attachment to the connective tissues. Thus each muscle is enclosed in a connective tissue sheath which continues beyond the ends of the muscles as a tendon. The latter is attached directly to a bone which may serve either as a lever for movements or as an anchor. Muscle tissue does work only when it contracts and the pull is translated to the moveable bone. Movements in opposite directions require that the muscles work in pairs. The members of a pair of muscles are so mounted that the contraction of one muscle causes movement in the opposite direction from that of the other. For example, adductor muscles on con-

traction draw the leg backward toward the long axis of the body, and the opposed abductor muscles draw the leg anteriorly. (Fig. 87.)

The structural and functional units of striated muscle tissue are the microscopic muscle fibers which are associated in great numbers to form the various muscles of the body. Each fiber is enclosed in a delicate connective tissue membrane and contains several nuclei. It is believed that each muscle fiber represents a greatly modified single cell, in which the original nucleus has divided several times without corresponding divisions of the cell body. The cytoplasm of the striated fibers exhibits both transverse and longitudinal striations, the former being much the more prominent. When contraction occurs, the alternating transverse bands become broader as the length of the fiber decreases. (Fig. 21*A*.)

Cardiac muscle tissue, which is localized in the walls of the heart, is regarded as a distinct type of muscle tissue though showing structural relationships to both smooth and striated tissues. Thus there is a distinct transverse striation, as in voluntary muscle; but on the other hand, the cardiac cells, though connected by cytoplasmic strands, retain their individuality much as in the unstriated tissue. (Fig. 12.)

Nerve Tissue

The beginnings of the specialized irritable nerve tissue in the animal body are found in simpler animals than those in which vascular tissue is first noted. Thus, in the tiny fresh-water polyp Hydra, differentiation among the outer ectodermal cells produces branching nerve cells with long processes which are receptive to stimuli and which also stimulate contractile cells in the body wall to coordinated movement. But increasingly, in the higher animal types, the highly differentiated cells of the nerve tissue are grouped together to form the most complex tissue system of the body and one that is possibly even more widely distributed than the elements of the vascular system. The cellular unit of nerve tissue is the neuron, which is always ectodermal in origin but develops into a variety of types essential to the various positions and functions assigned to them. Three main groups of neurons are recognized as follows: the *sensory neurons*, which are located in the skin and the various external and internal sense organs and serve as outposts for the reception of the infinitude of stimuli projected upon the organism; the *motor neurons*, which are concerned with stimulating the proper muscle elements; and the *adjustor neurons* (association or integrative) in the brain and spinal cord, which mediate between the sensory and motor neurons to bring about integrated

responses. Certain of the neurons of the brain cortex, primarily concerned with the higher mental processes, possibly constitute a fourth type of neuron. Structurally the cell bodies of every type of neuron are characterized by cytoplasmic processes of varying length and branching over which the nerve impulses travel. (Fig. 22.)

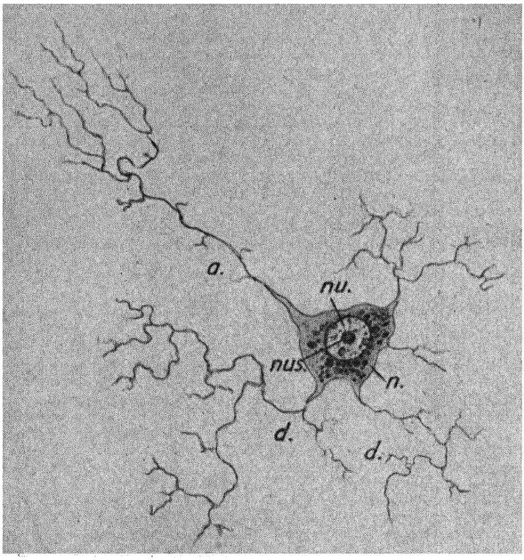


FIG. 22.—Nerve cell (neuron) from the central nervous system of a rabbit. Highly magnified. *a.*, axon; *d.*, dendrite; *nu.*, nucleus; *nus.*, nucleolus. (*Weber, Valentine.*)

ORGANS AND ORGAN SYSTEMS

The next step in the organization of the animal body beyond that of tissue development is the permanent association of various tissues to form definite structural and functional units, the organs. Examples of organs are to be seen in such commonly recognized parts of the body as the eye, heart, and stomach. An examination of any organ reveals the fact that it is built up not of one tissue alone but of several—a mosaic, as it were, in which each of the associated tissues has its characteristic assignments. However, it is also clear that in most organs one of the associated tissues is essential for the particular function assigned to that organ in the economy of the organism, whereas the other associated tissues of such an organ are accessory. Thus, for example, in the alimentary canal, the functional activities center in the nutritive epithelium which forms the inner lining and is responsible for the digestion and absorption of food. Associated with this essential nutritive epithelium to form the complete organ are other

accessory tissues, namely, muscle tissues in the wall which function in moving the food materials through the alimentary canal by peristaltic contractions; vascular tissue which receives the digested foods and transports them to all regions of the body; nerve tissue which controls and coordinates all the constituent tissues of the nutritive system; and, finally, the connective tissue elements which bind all the functionally associated tissues into a structural unity. (Fig. 32.)

Another good example of the association of diverse tissues in an organ may be found in the eye, in which the essential functional tissue is a very complex, inner layer of nerve tissue, the retina, on which the light rays impinge and act as a stimulus. In addition, the eye contains various accessory tissues including nerve fibers for conducting the stimuli received in the retina to the brain: the transparent lens, which focuses the light rays on the retina; the connective tissues forming the protective layers of the eyeball and permeating the retina itself to hold the functional units together; the muscular tissue responsible for the movements of the eyeball and also governing the amount of light admitted to the interior of the eye. Finally, all of the eye tissues are permeated with tiny branches of the vascular system. (Plate XIII, p. 229.)

One final stage in the organization of the well-developed animal body is found in the organ systems in which the organs associated with a particular function are grouped together for the performance of the essential functions of the organism. Thus, in man, we have the nutritive system, the respiratory system, the secretory system, the excretory system, the vascular system, the motor or muscular system, the skeletal system, the nervous system, and the reproductive system, all of which represent complete functioning units of the organism. Each of these organ systems will be found to consist of an assemblage of integrating structural units, or organs. Thus, in the vascular system, the heart is an organ of first importance functioning as a powerful pump, but the complete vascular system includes not only the heart but also the blood, the blood-forming tissues, and literally miles of tubes of different sizes through which the liquid blood is supplied to all the tissues. And so it is with all the organ systems.

In summarizing, it is seen that the human organism begins its individual existence as a single microscopic cell and, in time, becomes a multicellular unit with many billions of cells. And as the cells are increased in number, so are they increasingly set apart by differentiation to form the basic tissues of the body, and these, in turn, are further differentiated to form more and more specific types. But the tissues do not remain separated functionally; they group together to form

definite functional organs, which are linked to form the organ systems; the sum total of which comprises the complete organism.

THE BODY PLAN

Having considered the general organization of the living materials in the human organism, extending from cellular levels to organ systems, attention may next be centered on the complete structural plan of the human body. It is at once evident to the biologist that there is an underlying relationship to certain features first apparent in the animal world in the earthworm type of organism; that is to say, the human body does not exhibit a startling array of new anatomical features but

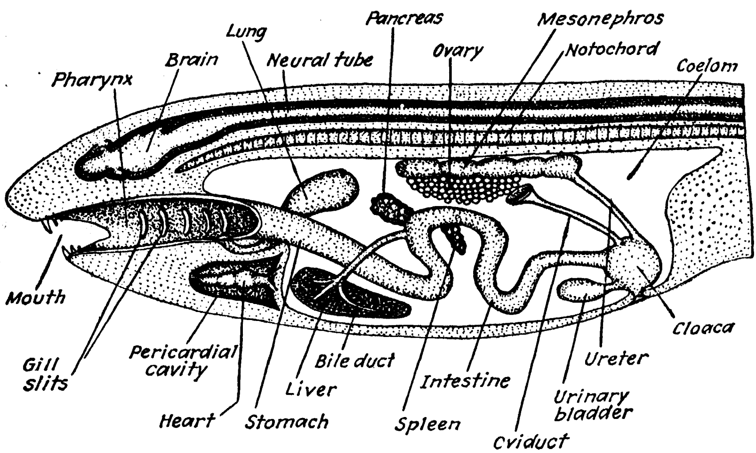


FIG. 23.—Body plan of a typical lower vertebrate, female, as seen in a median longitudinal section. Diagrammatic. (*Wolcott, after Wiedersheim. Redrawn with modifications.*)

rather modifications and further development of structural plans which the comparative anatomist has seen incompletely expressed in various of the lower types of animal life. Of particular importance are certain zoological landmarks shown at the earthworm level. These include the three-layered or *triploblastic condition* of the body in which the tissues are derived during development from three primary germ layers: ectoderm, endoderm, and mesoderm; the *coelomate type* of structure in which the body plan is best described as a tube within a tube, the outer tube forming the body wall and the inner, the alimentary canal; *bilateral symmetry* which is basically two-sided—right and left—with the organs, as a rule, developed in pairs and lying to the right and left of a median line so that only one plane divides the body into symmetrical halves; the *segmented body* with the

segments arranged in a linear series; and, finally, the grouping of tissues to form highly specialized *organs* and *organ systems.*

To these important landmarks in animal organization have been added, in the body of man, several other structural features that are characteristic of the vertebrates in general. There is, in the first place, an internal framework of supporting tissues, the endoskeleton, which reaches its climax in the formation of bone tissue. One of the principal parts of the bony endoskeleton is the vertical axis or backbone (vertebral column) built up of several segments (vertebrae) and with two pairs of jointed appendages attached to it. Then there is a dorsal, tubular nerve cord which receives protection and support from the vertebral column that encloses it. Finally, there is a four-chambered heart, lying ventrally. (Fig. 23.)

The human body is divided into two major divisions, the head and trunk, which are connected by a lesser division, the neck. The head consists of the facial portion, with terminal accommodations for the nutritive, respiratory, and sensory functions; and of the skull, or cranium, which is essentially a brain case. Comparatively speaking, the human head is noteworthy for a great increase in the size of the cranium and a corresponding reduction in the facial portion. Thus the horse has a facial portion several times the size of the human face, whereas the brain case is smaller than that of man. Vertebrate cephalization reaches a climax in man through the very extensive development of the forebrain and of the bony skull, which provides a complete rigid armor of great strength to protect the extraordinarily delicate brain tissues. (Fig. 102.)

The trunk region is naturally divided into the anterior chest region, or thorax, and the posterior abdominal cavity. Internally these two regions are separated in man and the higher vertebrates by a membranous sheet of tissue, the diaphragm. The thorax, containing the lungs and heart, is given over almost entirely to the respiratory and vascular functions. Considerable reinforcement of the body wall is attained in the thorax by the 12 pairs of encircling ribs, which provide a great deal of protection to the comparatively delicate and vitally important tissues of the heart and lungs. It may be noted that the ribs are also important in the respiratory movements that occur through the action of the attached muscles. The abdominal cavity contains the entire length of the alimentary canal except the small portion, the esophagus, which connects the throat region with the stomach. The esophagus passes upward through the diaphragm, above the stomach, then continues anteriorly through the thorax to the throat. Several other important organs are present in the abdominal cavity, notably

the liver, pancreas, spleen, and kidney, together with the major elements of the autonomic nervous system which is the controlling agent for the entire group. Bony tissue is lacking in the wall of the abdomen. The latter consists merely of the skin attached to the underlying muscles by the subcutaneous fibrous connective tissue, the various layers forming a resistant but not too rigid retaining wall for the enclosed organs. (Plate III, page 40 and Plate X, page 168.)

Attached to the trunk, or, rather, to the vertebral column in the trunk region, are two pairs of jointed, five-fingered appendages, the arms and legs, which are homologous with the appendages present throughout the vertebrate series. Although the vertebrate appendages are basically organs for locomotion, the erect posture of man, with bipedal instead of quadrupedal locomotion, has left the forelimbs free for the performance of a myriad of important duties to which they are remarkably adapted. Nowhere in nature is a more adaptable structural unit to be found. When the human hand is compared with the hoofed appendages of the horse and ox, the tremendous advantages that have accrued to man through the possession of his amazingly versatile hands become at once apparent. But even so, the quadrupedal type of locomotion would have largely nullified the uses of even so extraordinary a structure as the human hand. And it is also evident that the erect posture of man is of prime importance in that it has increased his outlook, as is indicated in the admonition to "keep head erect and look things straight in the face like a man." An erect body posture is not easy to maintain and requires coordinated control of numerous muscles under the continuous supervision of the nervous system. Maintenance of an erect position and the associated bipedal locomotion are learned by intensive effort in early life and then become an automatic function which, under normal conditions, is controlled involuntarily.

Head, neck, trunk, and limbs—these constitute the prominent external structural divisions of the human body. But, as already shown in the earlier pages of this chapter, the external characteristics give essentially no idea of the complexities present internally in the association of cells, tissues, and organs responsible for the inherent functional phenomena essential to life.

THE SKIN

Finally it will be worth while to focus attention upon a remarkable material, the skin, which forms the covering over practically the entire body and which possesses noteworthy properties essential to the underlying body structures. But the skin is far more than a resistant,

covering material, for it functions also in connection with temperature control, excretion, and as an efficient sensory organ equipped for the detection of a wide variety of environmental stimuli, so that the organism is able to keep in touch and adapt to the external conditions. Possibly above all else, the vertebrate skin stands as a tremendously effective barrier between the body and all sorts of destructive parasites which otherwise would invade the body tissues and produce disease. Very few disease-producing organisms are known which are able to penetrate the unbroken skin of the human body. (Fig. 24.)

Examined microscopically, the skin is found to be divided into two main portions: an outer epidermis and an underlying dermis, or corium.

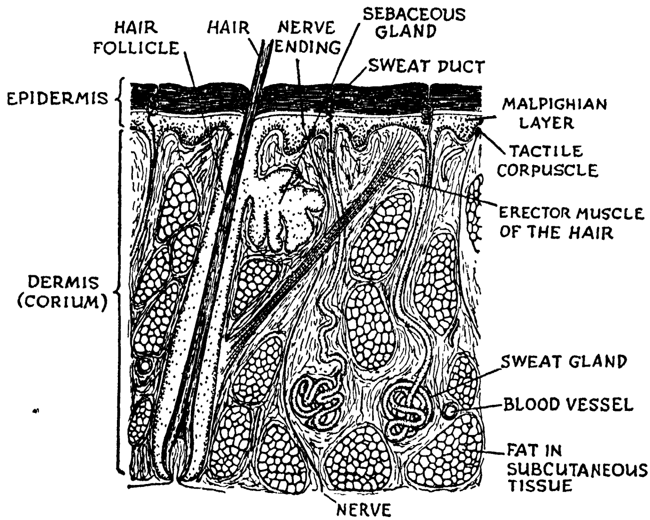


FIG. 24.—Mammalian skin as seen in a vertical section. Diagrammatic. Highly magnified. (*Redrawn from Wolcott.*)

Consider, first, the epidermis; it consists essentially of numerous layers of epithelial cells which adhere tenaciously to each other, though with a minimum of intercellular material, to form a resistant material suitable for contact with the environment. Continued examination of the epidermis reveals a rather clear differentiation into a relatively thick, horny outer region, below which is a thinner Malpighian region joining with the upper boundary of the dermis. The cells in the outer layers of the epidermis are very much flattened and are mostly dead anucleate bodies characterized by heavy cell walls, particularly on the palms of the hands and the soles of the feet where they are subject to almost continuous friction. The dead epidermal cells are constantly being shed, and new ones supplied from the underlying cells in the Malpighian region.

Tiny openings of the sweat glands perforate the epidermis in practically all regions of the body. It is estimated that a total of around 2½ millions of these openings occur in the entire body surface. They are most abundant in the palms and soles, where there are possibly 2,500 per square inch, and are fewest in number on the back of the body where an average of around 400 to the square inch is estimated. The body of a sweat gland, the secreting portion, lies deep in the dermis and is seen as a tiny sac-like structure surrounded by a net of blood capillaries. Thus the gland consists essentially of a fine tube, coiled at one end, and with the opposite end continuing as a straight tube to the external opening at the surface of the skin. The amount of liquid removed from the blood and released by the sweat glands is considerable, but both the quantity and composition of sweat varies a great deal under different conditions of temperature and activity, as will be seen later in considering the question of temperature control.

In contrast to the simplicity of the outer epidermis is the relative complexity of the underlying corium with its intimate association of vascular and nervous tissues, together with very numerous hair follicles in which the hairs are developed and nourished. Microscopic examination of a transverse section through the skin shows that the upper dermal boundary, lying in contact with the epidermis, is not smooth and regular in appearance but is raised in mound-like bodies which project into the lower layers of the Malpighian cells. Some of these dermal projections are occupied by networks of capillaries; others contain groups of sensory cells of the nervous system arranged to form tactile corpuscles. As a result, the dermis is highly vascular and also very sensitive to environmental stimuli. The main body of the dermis consists of a dense network of connective tissue fibers in which the various other tissues are embedded.

Forming an almost complete covering over the skin surface of the typical mammalian type is a coating of hair. In man, the hair forms a dense covering on the head, a thin covering on most other regions of the body and may be entirely lacking as on the palmar surfaces of the hands. Further consideration of the hair may be deferred until the later chapter (IX) on the Skeletal System. A difference in the character of the skin covering is clearly apparent on the lips and in association with other openings. Such differences, however, are more superficial than basic in character, for the microscopic examination of the mucous membranes, as these tissues are called, shows that the general plan of the skin tissues with outer epidermis and underlying corium remains essentially unaltered. But neither of these regions are so strongly developed in the mucous membranes, and accordingly

they are somewhat less resistant. In certain instances, as in the lips of the Caucasian peoples, the typically opaque outer epidermal layers are quite transparent, and so the underlying, highly vascularized dermal layer is revealed by the characteristic blood-red color. The mucous membrane does not stop at the entrance of the mouth but continues throughout the length of the alimentary canal as the epithelial lining (mucosa) which becomes specialized for the nutritive processes. Thus all of the tissues and organs of the body may be thought of as lying between the external covering of skin and the inner mucous membrane which lines the alimentary canal.

Lying underneath the skin and gradually merging with the connective tissue fibers of the corium is the layer of subcutaneous connective tissue which binds the skin to the underlying muscle tissues of the body wall. Subcutaneous tissue consists largely of bundles of white fibrous tissue. They are continuous both with the connective tissue of the corium above and with that which penetrates the deeper lying tissues. The connective tissue elements of the subcutaneous tissues are loosely arranged with plenty of space for nerves and blood vessels, and this condition also permits the skin considerable freedom of movement. In certain regions, however, notably in the soles of the feet, the skin is more firmly attached, and here it will be found that the subcutaneous tissues are heavier and more compact. One of the characteristic features of the subcutaneous layer is its ability to store reserve fat in modified connective tissue cells. This condition is particularly evident in the subcutaneous tissue of the ventral abdominal region and often results in a marked accumulation of fatty tissue.

Removal of the skin and the subcutaneous tissue from almost any portion of the body reveals an essentially unbroken layer of muscle tissue. Connective tissue elements permeate through the muscles and separate them into definite units as has already been indicated (page 27). Thus the connective tissues bind together the skin, muscles, bony skeletal structures, and associated vascular and nerve components in an essential structural unity. Perhaps this condition is most clearly evident in a definite motor unit such as the leg, but it is no less a fact in other organs of the body.

With the general plan of the body in mind, as indicated in the previous pages, the way is cleared for a study of the various organ systems, essential to the maintenance of life in the individual. In the present volume, consideration is given to the nine primary organ systems responsible for the functions of *nutrition, respiration, secretion, excretion, transportation, contraction, support, irritability,* and *reproduction.*

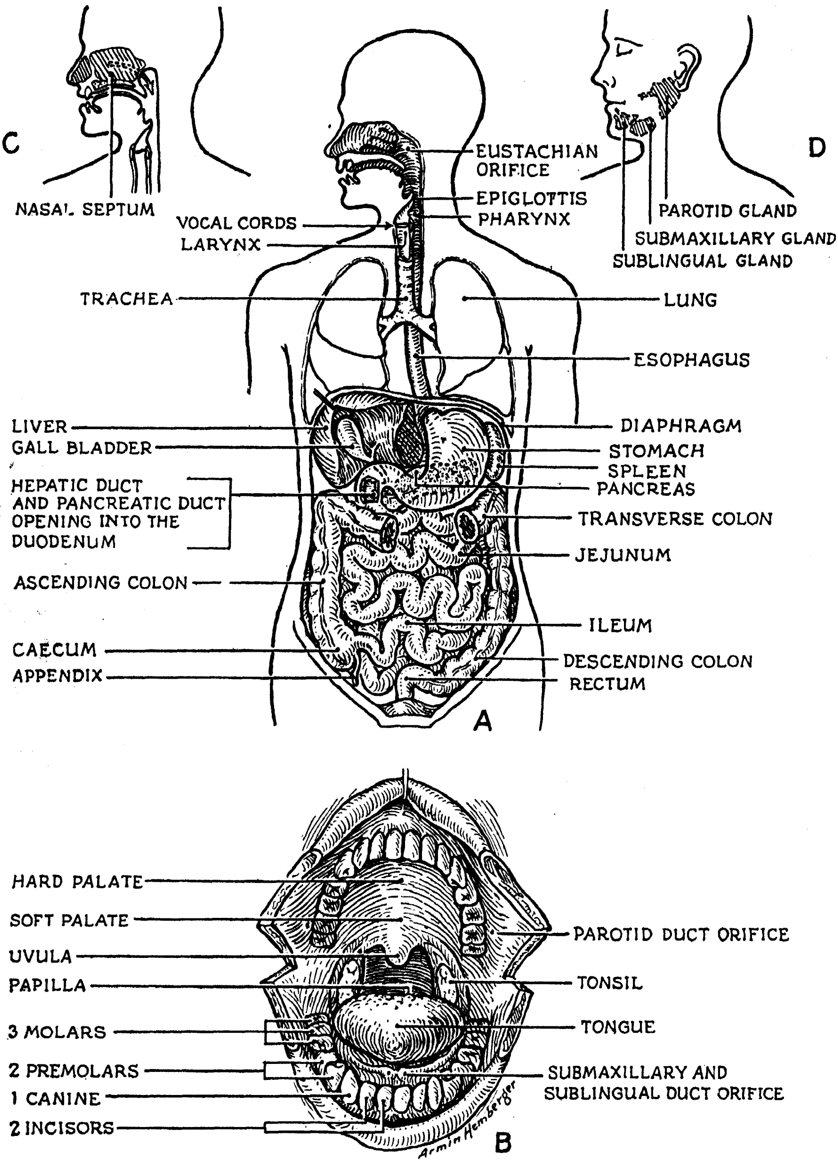


Plate III.—The nutritive system of man. Somewhat idealized. *A*, digestive tract; *B*, mouth cavity; *C*, region of the pharynx; *D*, salivary glands, left side.

CHAPTER III

THE BIOLOGY OF NUTRITION

Man as a living organism requires a constant supply of energy in order that the "wheels of life" may be kept continuously revolving. Materials must be available also for the repair and for the growth of the bodily structures. Both of these requirements must be supplied from the food that is taken into the body. Furthermore, we know that the mere ingestion of food materials will not suffice, because they cannot be utilized until properly prepared. They must undergo chemical change—the process of digestion—before they can be absorbed and assimilated by the cellular units that make up the organism. *Digestion, absorption, assimilation*—these are the nutritive processes that form the basis of our discussion in the present chapter.

STRUCTURAL FEATURES ASSOCIATED WITH NUTRITION

From the comparative standpoint, the foundations of the highest types of nutritive apparatus, as found in man, are to be seen in the primitive multicellular hydra with its permanent diploblastic condition in which an outer layer of ectoderm forms the body covering and an inner layer of endoderm lines the simple enteric cavity where the food is digested. For, in the embryonic condition of the higher animal types, a hydra-like stage occurs in which the newly formed endoderm is permanently assigned to the nutritive function. This two-layered stage is quickly followed in the embryo by the permanent three-layered, or triploblastic, stage in which the important mesoderm layer develops between the ectoderm and endoderm, but the addition of the mesoderm does not affect in any way the position or function of the endoderm; the latter forming the nutritive epithelium which remains throughout life as the essential functional layer lining the alimentary canal throughout its length. (Fig. 25.)

The enteric cavity of the primitive hydra is essentially a blind sac with a single opening which serves for the ingestion of food and for the egestion of the refuse. But the more advanced earthworm type has an anterior mouth opening and a posterior anal opening. Thus the nutritive apparatus, with its endodermal lining, becomes a tubular structure extending the length of the body through which the

food is propelled by peristaltic contractions of the muscular wall. The growth of the mesoderm layer during development separates the ectoderm and endoderm of the body wall. Finally, the mesoderm divides into an outer and an inner layer to form the permanent body plan which may be described as a tube within a tube; the inner tube consists of the alimentary canal with endodermal lining and mesoderm outside, and the outer tube, with ectodermal covering and mesoderm inside forms the body wall. The body cavity, or coelom—an important landmark in animal structure—lies between the two

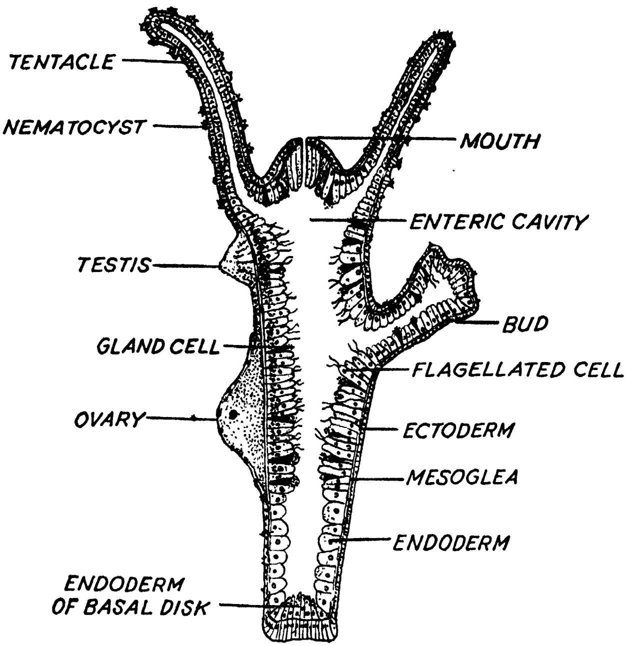


FIG. 25.—Longitudinal section through the metazoan,[1] Hydra, to show the primitive nutritive, or enteric, cavity. (*After Kepner and Miller, redrawn.*)

tubes. This type of alimentary canal remains as the permanent type in all the higher animals, and the variations in the nutritive mechanisms that are found in the various animal groups are primarily associated with adaptive features essential to particular food requirements rather than to a change in the basic plan. (Fig. 26.)

Typically, the vertebrate alimentary canal, as in man, is separable into seven primary regions which, beginning anteriorly, are as follows: the mouth, or buccal cavity; the throat, or pharynx; the gullet, or esophagus; the stomach; the small intestine; the large intestine; and the rectum. In addition, there are a number of associated glands

[1] Consult the Appendix: Metazoa.

which give off their secretions into the alimentary canal through the attached ducts. (Plate III*A*, page 40.)

Mouth

The mouth, as the specialized anterior end of the alimentary canal, is, of course, primarily concerned with the intake of food, but it shows wide variation in the various vertebrates, from a comparatively undifferentiated cavity with a slit-like opening to a highly developed masticating, tasting, digestive organ with oratorical proclivities as seen in man. Geographically speaking, the human mouth cavity may be said to be bounded in front by the flexible muscular lips; laterally by the cheeks; dorsally by the immovable, bony, hard palate; below by

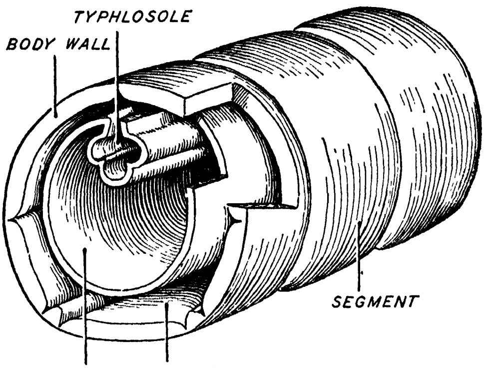


Fig. 26.—Transverse section of the earthworm, illustrating the "tube within a tube." Diagrammatic. (*Buchanan, "Elements of Biology," Harper & Brothers.*)

the movable lower jaw with its bony framework, attached soft tissues, and median tongue; and posteriorly by the throat region with which it merges. In the throat region, the hard palate is replaced by the soft palate, supported on each side by a pair of muscular pillars and prolonged into a fleshy teat-like median structure, the uvula. The soft palate, pillars, and uvula converge when food is being swallowed and thus form a fleshy partition between the mouth and throat cavities. (Fig. 27.)

The most prominent structures in the mouth are the teeth and tongue. The consideration of the former may well be deferred until the skeletal system is described. It is sufficient to note at this point that the teeth are efficient tearing and grinding organs which have the ability, if properly used, to break up the solid food masses to such a degree that digestive juices can begin their action without delay. Proper mastication is particularly important in the case of plant tissues

because the abundant cellulose material is very resistant to the digestive juices. But the complete process of mastication is not wholly a function of the teeth; both the tongue and the cheek aid in manipulating the food mass and in keeping it between the grinding apparatus.

The body of the tongue is composed of striated muscle tissue, with the fibers running in all three planes and with intermingled connective tissue elements. It is a highly flexible structure admirably adapted for aiding in speech; in fact, it is essential for the production of various letter sounds. But the tongue is really not responsible for speech and is, therefore, not the "unruly member" of the body, as often designated. Sounds associated with the talking function have their origin primarily in the vibrating vocal cords of the voice box, or larynx, and are a by-product, so to speak, of the mechanism for breathing.

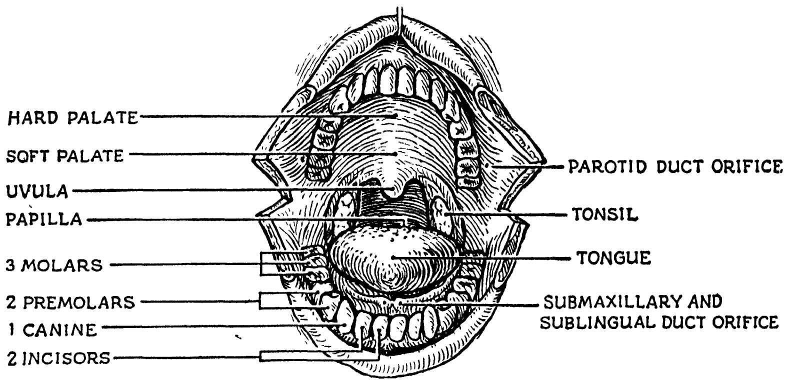


FIG. 27.—The mouth, or oral, cavity of man. The upper and lower jaws are separated more than normal to show all the structures.

The tongue is covered by a well-formed mucous membrane which is smooth underneath but notably rough on the upper surface. Considerable areas of the upper surface, particularly toward the back of the mouth, are covered with a highly modified mucous membrane, which is essentially a sensory epithelium associated with the sense of taste. It presents a surface studded with numerous slightly elevated circular areas, the papillae, containing many tiny barrel-shaped pits, the taste buds. The latter are present on the sides of the papillae rather than on the upper surface. In each of the taste buds is a group of sensory neurons, with associated supporting cells. These neurons are the essential taste cells and are connected by tiny nerve fibers to the nervous system. (Fig. 116.)

It is clear that many so-called tastes are due to a combination of taste and smell. This fact is quickly evident when one has a head cold and the olfactory sense is greatly reduced. Under such con-

ditions, the sense of taste disappears to a large extent though the neurons of the taste buds are not directly affected. It is generally recognized that only four primary tastes really exist, namely, sweet, bitter, sour (acid), and salt. All the very numerous other gustatory sensations appear to be combinations of taste and smell.

Opening into the mouth cavity are numerous small buccal glands which are widely distributed in the lining membranes, but the characteristic and abundant mouth fluid, saliva, is largely the product of three pairs of glands of considerable size, namely, the parotid, submaxillary, and sublingual glands. The ducts of the two pairs last named open in the floor of the mouth, almost directly below the tip of the tongue, and the bodies of these glands are situated laterally on each side and toward the back of the mouth cavity. The pair of parotid glands is the largest of these so-called *salivary glands*, and each lies embedded in the cheek tissues in front and to some extent below the tip of the ear. The ducts of the parotids continue forward along the upper jaw and open on each side, opposite the second molar. (Fig. 28.)

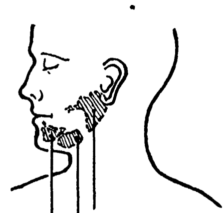


FIG. 28.—Human salivary glands. Drawing shows glands on left side only. Openings indicated in Fig. 27.

Saliva, the composite product of the salivary glands, is a liquid substance with a characteristic slimy or stringy quality due to the presence of a proteinaceous lubricant, mucin. Saliva consists principally of water with some mucin and other protein substances, inorganic salts, and, particularly, a digestive enzyme, ptyalin,[1] in solution. Ptyalin acts specifically on the carbohydrates and begins their digestion in the mouth as the food is being chewed.

THROAT

In the journey of the food materials through the alimentary canal, the next station is the throat region, or pharynx. This may be regarded as an important transfer point, or junction, used jointly by the nutritive and respiratory systems. The food materials scarcely delay at all in their passage through the throat, and no additional nutritive processes occur. It is simply a question of making the right connection so that the food will reach the stomach by way of the gullet and thus prevent even the tiniest particle from being wrongly directed so that it invades the windpipe, or trachea, leading to the lungs. (Figs. 29, 30.)

[1] Ptyalin is also known as *salivary amylase*.

ltogether, there are seven separate openings into the throat. These consist of two openings of the nasal cavities; two openings of the Eustachian tubes which lead to the middle-ear region; an opening (glottis) into the trachea; an opening into the gullet; and, finally, an opening from the mouth to the throat. It is easy to see how an infection in the throat region may spread widely through the body. Particularly susceptible to throat infections are the nasal region, the trachea of the respiratory system leading to the lungs, and even the cavity of the middle ear, the infection coming through the Eustachian tubes. It is also apparent that the food materials passing through the throat en route to the gullet must be accurately directed.

The mass of chewed food, or bolus, resting upon the back part of the tongue, is pushed into the throat region by coordinated tongue movements, the soft palate with the attached uvula being elevated during this process. Projecting upward, or anteriorly, from the aperture of the ventrally situated trachea is the flexible epiglottis, cartilaginous in nature. During the passage of the air in or out of the lungs, the epiglottis stands erect, leaving the tracheal opening unobstructed, but when food passes from the mouth to the throat, the erect epiglottis is pushed back and down by the oncoming mass, thus closing the respiratory passage through the trachea and permitting the food to pass over the "epiglottis bridge" and into the opening of the gullet lying dorsally. At the same time, the tissues of the soft palate act in such a way as to prevent any of the food from passing up into the openings of the nasal cavities or back into the mouth.

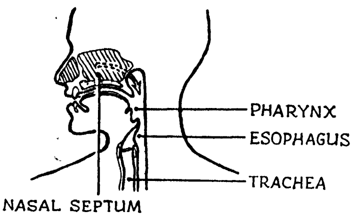


FIG. 29.—Illustrating the various openings into the throat, or pharynx, of man.

This complicated arrangement for the directed movements of the food masses through the common throat passage functions efficiently unless, unfortunately, as not infrequently happens, a person starts to laugh or to say something as the food is passing over the epiglottis. If this happens, the epiglottis is forced up by the pressure of the outgoing air, and some food particles enter the respiratory passage. Immediately a violent contraction of the respiratory muscles is incited, and air under high pressure is forced from the lungs and through the trachea in an endeavor to expel the foreign particles without delay. Almost invariably this succeeds, but instances are not unknown where a person has choked to death before the obstruction could be removed. Swallowing is not a haphazard process but a carefully planned

series of events which function perfectly unless interrupted by carelessness.

The Esophagus, or Gullet

The esophagus, which connects the throat with the stomach, is a muscular walled tube structurally specialized for the rapid conveyance of food to the stomach. Although glandular tissues are present in certain regions, no digestive enzymes are secreted. The esophagus is about 15 in. long in man and very distensible, but wide variation occurs in different animal types depending upon the length of the neck. Thus, in a long-necked giraffe, the esophagus is several feet in length. In birds, the structure of the esophagus is complicated by the development of a storage sac, or crop, in which the unchewed foods are temporarily stored before passing on to the stomach (gizzard) which is equipped for grinding. (Fig. 30.)

It is important to note that the muscular tissue in the walls of the esophagus, as in the remainder of the alimentary canal, is very largely smooth, or involuntary. Swallowing is a voluntary act; but when the food is finally and carefully placed in the opening of the esophagus, it passes from voluntary control, and involuntary peristalsis is then responsible for the movements of the food through the remainder of the journey. Peristalsis, under normal conditions, is a slow-traveling wave of contraction which moves posteriorly, reducing the diameter of the alimentary canal as it goes and thus forcing the contents of the intestine along ahead of it. A more rapid and powerful peristaltic action may be seen in the esophagus of a horse when drinking from a low-lying trough or brook. Even in man, peristalsis may be speeded up, or the direction of contraction may be reversed, as when the stomach gets "upset," and the contents are regurgitated through the mouth.

The Stomach

The human stomach is roughly conical in shape with distensible muscular walls lined by the essential nutritive epithelium, or mucosa. It has a capacity of approximately 2 qt. at its minimum size but is capable of considerable temporary enlargement. The stomach lies in the abdominal cavity, just below the diaphragm, in close proximity to the liver. It is situated well to the left of the median line with its long axis more or less transverse to that of the body. The larger portion of the stomach, or what might be termed the base of the cone, points upward and to the left and is almost in contact with the under surface of the diaphragm. This region is designated as the *cardiac*

portion, or *fundus*. Here the esophagus opens into the fundus through its upper surface. Esophageal muscle fibers extend for some distance into the wall of the stomach before losing their identity. From the fundus, the stomach curves markedly toward the right side of the body and gradually tapers down to the tip of the cone where connection is made with the small intestine. This is the *pyloric portion* (*pylorus*) and it terminates in a specialized ring of tissue, the pyloric valve, which guards the entrance to the small intestine. (Fig. 30.)

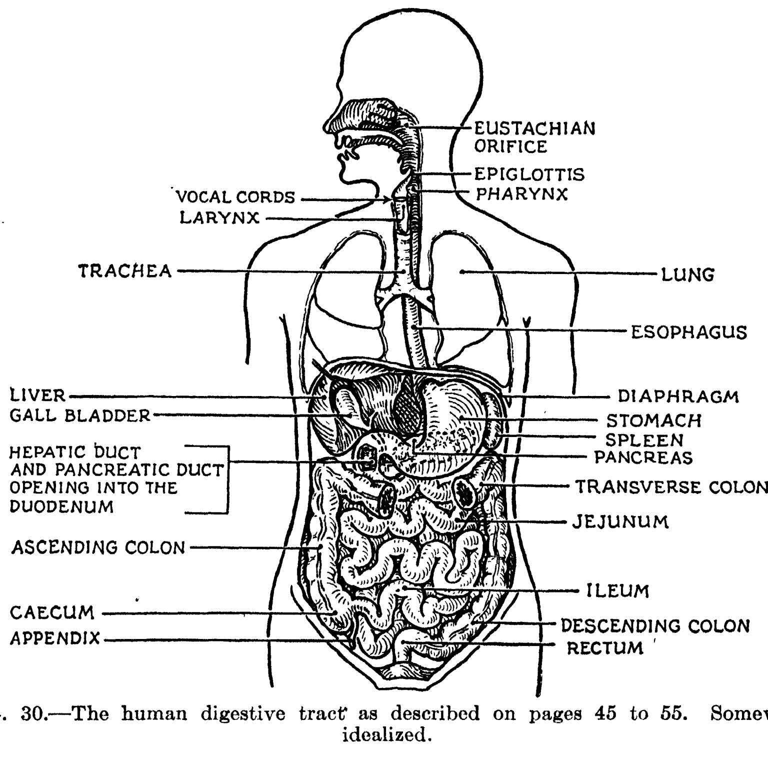


FIG. 30.—The human digestive tract as described on pages 45 to 55. Somewhat idealized.

Commonly regarded as the most important organ of the digestive system, the stomach, as a matter of fact, is not so important for the essential digestive processes as it is for its services as a mixing and homogenizing organ for the diversified foodstuffs that pour into it after their rapid descent by the peristaltic elevator through the esophagus. The motility of the stomach walls is very great, as is well shown by X-ray pictures taken during the digestive processes. Repeated waves of peristalsis move from the cardiac portion, where the food is received from the esophagus, toward the pylorus. Separate

waves of peristalsis originate in the pylorus walls and move towards the pyloric valve. As many as three distinct waves of contraction may be noted moving over the stomach walls at the height of the process. The pyloric valve, guarding the entrance into the intestine, remains closed until the food is thoroughly churned. Then it gradually relaxes in response to the repeated contractions coming from the pylorus and permits small amounts of the food mass, now a liquid, chyme, to move into the intestinal regions for the final stages of digestion and absorption.

The mucosa forming the lining of the stomach is highly **glandular.** It is estimated that as many as 35 million microscopic gastric **glands** pour their secretions into the stomach cavity, and the total amount **of** daily secretion varies around 1½ qt. Several types of gastric gland are recognized by the histologists, but essentially all of them may be said to be simple tubular structures which penetrate the mucosa perpendicularly to the surface, and so their secretion passes directly into the stomach cavity through these tiny openings. Three or more types of secretory cell may occur in these glands. Gastric juice, the composite product of the gastric glands, is a clear fluid, mostly water, but decidedly acid since it contains about 0.4 per cent hydrochloric acid. At least two important digestive enzymes are present in the gastric juice: pepsin for digestive action on the proteins, and rennin which coagulates the proteins of milk. The determination of the exact origin of the two gastric enzymes and also of the hydrochloric acid secreted in the stomach from among the three types of secretory cells has proved to be a difficult problem. And it is still a mystery how the mucosal secretory cells are able to form hydrochloric acid from the materials brought to them by the alkaline blood plasma. (Fig. 32.)

The Small Intestine

The small intestine of man is a greatly coiled tube, about 1½ in. in diameter and some 20 ft. in length. It joins the pyloric region of the stomach through the pyloric valve, a little to the right of the median body line and about midway between the ventral and dorsal surfaces of the abdominal cavity. The portion of the small intestine attached to the stomach is known as the duodenum, and it continues about 12 in. and is succeeded by the jejunum. The latter has a length of about 9 ft., and then comes the ileum which makes up the remainder of the small intestine and extends about 10 ft. to its connection with the large intestine. The junction between the small and large intestines takes place through the ileocaecal valve which is situated in the

lower right-hand corner of the abdominal cavity, just above the pouch-like caecum. (Fig. 30.)

Mention should be made at this time of the supporting membranes, or mesenteries, which hold the stomach, intestines, and other viscera in place and also completely cover them with a delicate tissue, the serosa, so that they do not really lie exposed in the abdominal cavity. Essentially, the mesenteries are continuous with the mesodermal epithelium, the peritoneum, which lines the body wall of the abdominal cavity. This peritoneal lining is reflected from the dorsal

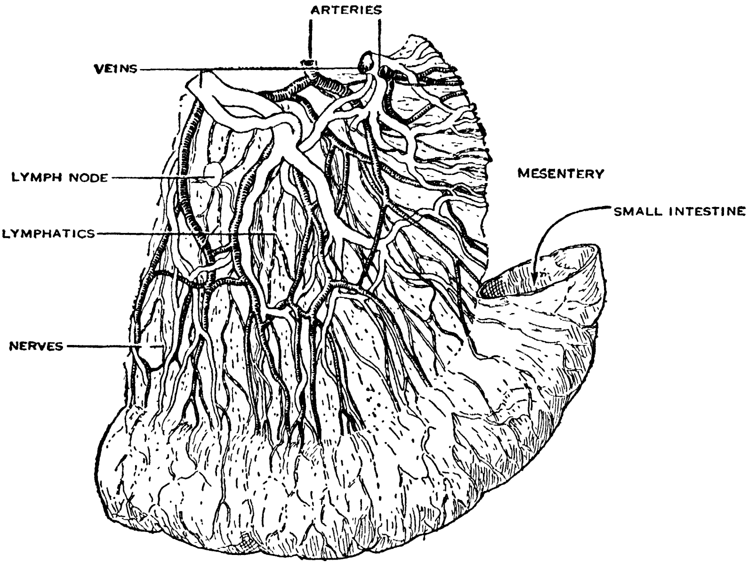


Fig. 31.—Portion of the small intestine of man, showing attached mesentery with its abundant vascular and nerve supply. Arteries, dark; veins, light. (*Haggard, "Science of Health and Disease," Harper & Brothers.*)

wall along the median line and encloses the alimentary tract in such a way as to hold the various parts in definite positions. The omentum is the largest of the mesenteries associated with the alimentary canal and hangs suspended from the stomach as a curtain-like membrane, ventral to the intestines. A similar material, the pleura, lines the thorax and is reflected over the lungs and heart. (Figs. 31, 32.)

A microscopical examination of a prepared section through the wall of the small intestine shows that it is composed of several distinct tissue layers. This same condition obtains with considerable uniformity throughout the entire length of the alimentary canal—such modifications as occur being for the most part found in the nutritive epithelium and in accordance with the functional demands of the

various regions. The first layer to be noted externally is the thin layer of serosa which, as just noted, is a membranous tissue directly continuous with the peritoneum and the mesenteries. Below the serosa come two distinct layers of smooth muscle tissue. In the outer one of these, the fibers run longitudinally, that is, lengthwise of the intestine, whereas the fibers of the inner muscle layer run in a circular fashion around the intestine. It is the progressive contraction of the circular layer that is essential to peristalsis. Within the muscular tissue is a layer of loosely arranged connective tissue, the submucosa, which is plentifully supplied with vascular and nervous elements.

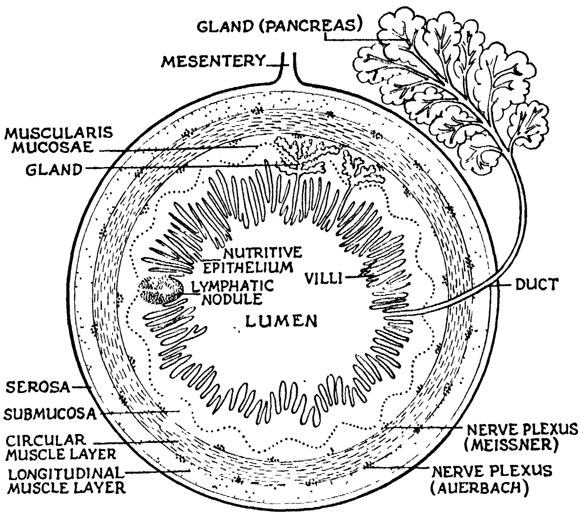


FIG. 32.—Diagram of a transverse section through the vertebrate intestine, duodenal region. Only two of the intestinal glands are shown. (*Redrawn from Maximow-Bloom, "Histology," W. B. Saunders Company.*)

Finally, we reach the essential functional lining layer, the nutritive epithelium, or mucosa. (Fig. 32.)

The nutritive epithelium of the small intestine follows the same general pattern as it does in the stomach, as described above, with the added fact that the mucosa of the intestine is more highly differentiated in keeping with its increased digestive and absorptive functions. In the first place, the lining mucosa does not present a smooth surface but is characterized by irregular circular folds which project a considerable distance into the lumen of the intestine. These folds greatly increase the area of effective mucosal surface and are such as would be formed if the mucosa lining the intestine were too long for the other intestinal layers that enclose it, and so, instead of fitting smoothly

inside when pushed into place, it is thrown into irregular projections. (Fig. 33.)

Covering the surface of the projecting folds of the mucosa, as well as in the spaces between the folds, are microscopic, finger-like projections, the villi, which function primarily in the absorption of the digested foodstuffs. Internally, the villi contain connective tissue elements and an abundant network of capillaries through which the absorbed food is carried from the intestinal region to the outlying districts. Also present in each villus is a thin-walled lymph vessel, the lacteal, which connects with a special division of the vascular system, known as the *lymphatic system.* The lacteals are largely concerned with the absorption of fats. The mucosa on the outer surface of the villi, that is, the surface in contact with the food, consists of secretory and absorptive cells, the latter for removing the food from the canal after it has been digested. Both these types of cell represent modified mucosal cells. The absorptive cells are long columnar cells with a granular cytoplasm. Microscopic examination does not reveal any noteworthy structural characteristics adapting them for their absorptive function. Nevertheless, these cells continually absorb large quantities of the digested foodstuffs from the alimentary canal and transfer them to the blood stream. (Fig. 34.)

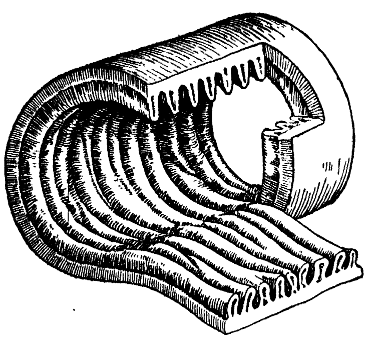


FIG. 33.—Section of the small intestine of man, showing the circular folds in the mucosa. (*Buchanan, "Elements of Biology," Harper & Brothers.*)

Intestinal Secretions.—The secretory cells of the villi are the unicellular goblet cells, so named because of their shape. Each goblet cell has an oval-shaped vacuole lying in the cytoplasm in which liquid mucus is constantly formed and then secreted into the digestive cavity. The secretion of the goblet cells apparently does not contain digestive enzymes, but it forms a protective covering over the mucosal tissues. The digestive enzymes appearing in the intestinal juice are secreted by other gland cells present in distinct tubular glands, the glands of Lieberkühn, which are essentially similar in structure to

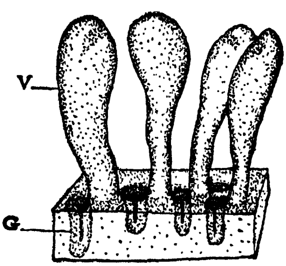


FIG. 34.—Diagram showing the lining of small intestine with projecting villi. Highly magnified. *G*, intestinal gland opening near base of a villus (*V*). (*Wieman.*)

those previously noted in the walls of the stomach. The glands of Lieberkühn are embedded in the intestinal wall between the bases of the villi and contain at least two distinct types of secretory cell which are responsible for the digestive enzymes present in the intestinal juices. The latter are formed in great abundance, possibly as much as 3 qt. per day, and contain several important digestive enzymes. These include the erepsin group and the enterokinases which are concerned with protein changes; lipase for the digestion of fats; and maltase, lactase, and sucrase which act upon the carbohydrates.

But the intestinal secretion is not the only enzyme-containing fluid in the small intestine, nor, in fact, is it the most important. That distinction belongs to the pancreatic juice which is poured into the pyloric end of the duodenum through the pancreatic duct. Secretions from the liver also enter the intestine near by. The structural and functional features of pancreas and liver are fully considered in the later chapter dealing with Secretion, but it will be helpful at this point to indicate the nature of the products of these organs so far as they are concerned with digestion. The secretion of the pancreas is a clear fluid, markedly alkaline in nature with a pH of about 9.[1] It contains three enzymes associated with the digestion of every type of foodstuff, including trypsin for the proteins, amylase for the starches, and lipase for the fats. The liquid received from the liver is a heterogeneous mixture, termed *bile*, and varying in color from golden yellow to dark green. It is usually somewhat alkaline and contains lipoids, various pigments (notably bilirubin which results from the destruction of old red blood corpuscles), and bile salts which are used in connection with the digestion of fats.

Thus the complete intestinal fluid, with the combined contributions from the mucosa of intestine and from both the pancreas and liver, contains all the substances essential for the completion of digestion of all types of foodstuff.

The Large Intestine

The large intestine, or colon, starts with the caecum, which is situated in the lower right-hand corner of the abdominal cavity. Just anterior to the caecum is the ileocaecal valve guarding the aperture of the ileum which perforates the wall of the large intestine at this point. The location of this opening from the ileum into the

[1] The symbol pH is commonly used to indicate the hydrogen ion concentration in solutions. A pH of 7.0 is a neutral solution. Values of pH below 7.0 indicate increasing acidity, whereas values above 7.0 indicate increasing alkalinity. Consult the Appendix, Hydrogen Ion Concentration, for additional information.

colon does not seem to be ideal because it leaves a blind sac, the caecum, lying posterior to it into which some of the intestinal contents, largely indigestible, from the small intestine may be sidetracked. Projecting posteriorly from the lower end of the caecum is the small tubular vermiform appendix, which not infrequently has to be removed surgically following infection and inflammation. (Fig. 30.)

The entire colon is about 5 ft. long and somewhat larger in diameter than the small intestine, approximating 2½ in. It is divided into three main regions known, respectively, as the *ascending* colon, the *transverse* colon, and the *descending* colon. The ascending colon begins with the ileocaecal valve and extends anteriorly along the right side of the abdominal cavity until it approaches the diaphragm. Here it turns abruptly to the left and, as the transverse colon, crosses to the left side of the abdominal cavity, lying close to the ventral body wall and almost directly above (ventral) the pyloric region of the stomach. Another abrupt turn posteriorly marks the beginning of the descending colon, which continues along the left side of the abdominal cavity until it almost reaches the posterior border where it turns dorsally and merges into the rectum. The latter continues to the external opening, the anus. The rectal and anal regions exhibit various structural features associated with the egestion of the fecal material. (Fig. 30.)

The microscopic anatomy of the large intestine reveals the characteristic five-layered type of wall described above for the small intestine, but certain differences are to be noted. Thus the wall of the large intestine is seen to have irregular constrictions giving it a peculiar puckered appearance externally. Internally, these constrictions result in the formation of lateral cavities which are partially cut off from the main central intestinal cavity. This structural arrangement appears to be a measure to increase the absorptive surfaces. It is due to the presence of longitudinal muscle fibers in the intestinal wall which are shorter than the associated tissues. The fibers consist of three longitudinal cables grouped in a median dorsal line and visible as a distinct ridge.

The mucosa lining the large intestine, unlike that in the small intestine, is essentially smooth, and projecting villi are lacking. However, absorptive cells line the comparatively large mucous glands which are present in great numbers in the mucosa. The function of absorption in the colon is very important, but it is largely concerned with the removal of excess water from the intestinal contents. The latter enter the large intestine as a rather thin liquid and finally leave it, after the water has been gradually absorbed, as solid fecal material. The total secretion per day of the mucosal glands of stomach, intes-

tine, liver, and pancreas total approximately 4 qt., most of which is water, and this amount, together with that lost through other channels, must be recovered or the deficiency supplied by drinking more liquid.

FUNCTIONAL FEATURES ASSOCIATED WITH NUTRITION

With the main structural features of the "tubular chemical laboratory" in mind, as just indicated in the previous section, consideration may now be given to the important functional features of nutrition in an endeavor to see how the ingested food materials are chemically changed during digestion and thereby made ready for the absorption into the body, transportation through the body, and final assimilation by the individual cellular units.

Foodstuffs

If we define a food as "any substance that, when ingested in the proper amount, is absorbed from the gastro-intestinal tract and contributes to the maintenance of the normal state of the body," a considerable variety of organic compounds will be included belonging to the carbohydrates, fats, proteins, and vitamins: also various inorganic compounds and elements, notably salt and water—the latter being by far the most abundant of all the body materials. However, when one considers the infinite variety of inorganic and organic compounds known to the chemist, built of the same common elements as those which are used in the construction of the body tissues, it is apparent that comparatively few are suitable for use as food by the human organism. One basic reason for this condition is undoubtedly the fact that the human digestive system is equipped with a limited number of digestive enzymes, and these are adapted for the digestion of relatively few substances.

Carbohydrates.—The carbohydrates are compounds of carbon, hydrogen, and oxygen and include three related groups of compounds, namely, the simple sugars (monosaccharides), commonly represented by glucose and fructose, with the molecular formula $C_6H_{12}O_6$; a more complex group of sugars, the disaccharides, represented by sucrose (cane sugar), maltose, and lactose, with the formula $C_{12}H_{22}O_{11}$; and the most complex carbohydrate group of all, the polysaccharides, represented by starch, cellulose, and glycogen (animal starch) with the formula $(C_6H_{10}O_5)_x$. Of these three groups, only the monosaccharides are absorbed from the digestive tract unchanged and so are ready to be assimilated at once by the body cells and oxidized as necessary to supply energy requirements. As will be shown below, digestion of any of the other carbohydrates reduces them also to the

monosaccharide type. Thus during digestion each disaccharide molecule is transformed into two molecules of the monosaccharide. A digestible polysaccharide, such as starch, requires more extensive digestive action, but the end result is the same, that is, the production of a simple sugar which can be absorbed. Unfortunately, it would seem, the human digestive apparatus is unable to digest one of the most noteworthy of the polysaccharides, cellulose, the most abundant of all plant materials (p. 510).

Fats.—The fats, or hydrocarbons, belong to a large and rather heterogeneous group of organic compounds, known as the *lipoids.* The grouping of the lipoids is on the basis of their solubility characteristics rather than their inherent chemical nature. Thus all of them are soluble in alcohol or ether. Also lipoids have a peculiar reaction to the skin; they feel greasy to the touch. Various kinds of lipoid are found in all the body tissues and are believed to be important constituents of the protoplasmic molecule. Some of the important lipoids are the fatty acids, the fats and oils, the sterols, and the phospholipins. Of these, the fatty acids form the most important group and may be regarded as the building stones of the fats just as the amino acids are the building stones of the proteins (page 70). Fats are formed by the union of a fatty acid and glycerine. Both the fatty acids and true fats are compounds of carbon, hydrogen, and oxygen, but the proportion of oxygen is much less than it is in the carbohydrates. This is particularly true of the fatty acids, which typically contain only a very few atoms of oxygen. Thus in stearic acid, with the molecular formula of $C_{18}H_{36}O_2$, it is seen that only two atoms of oxygen are present in the entire molecule. Inasmuch as both the fats and carbohydrates are oxidized in the body to yield energy, and since the end results of the oxidative processes is the same with both compounds, namely, the formation of carbon dioxide and water, it follows that more oxygen is needed for the oxidative processes when fats are burned in the tissues.

The body tissues store up fats whenever an excess supply of nutritive materials is taken into the body. By the proper chemical changes, either carbohydrates or proteins may be converted into fat for storage and accumulated in the subcutaneous tissues over the body or in association with various organs, notably around the kidneys.

Proteins.—By far the most complex and diverse group of the organic compounds is the proteins. They are characterized by the presence of nitrogen and sulphur in addition to the carbon, hydrogen, and oxygen of the carbohydrates and fats. Proteins usually contain a number of other elements, notably phosphorus, calcium, and

magnesium. A typical protein contains about 50 per cent carbon, 25 per cent oxygen, 16 per cent nitrogen, 7 per cent hydrogen, with the remainder consisting of sulphur, phosphorus, and various other elements. Proteins are formed by the union of the somewhat simpler amino acids, some two dozen of which are known (page 70). The amino acids are characterized by a particular grouping of nitrogen and hydrogen in the molecule of the acid indicated by the symbols NH_2 (amino group). When excess proteins are eaten, as frequently occurs in the average diet, the liver cells are able to remove the NH_2 group—the process of deaminization—from the excess amino acids, resulting from the protein digestion. The final result of deaminization is the formation, from the excess amino acids, of a carbohydrate that can be used to supply the energy requirements of the body or converted into fat for storage if the energy requirements are supplied, just as any other carbohydrate. The exact composition of the proteins, which build the cytoplasm of the different types of cells of the body, is highly variable due to the fact that each cell selects the proper amino acids and other substances from the blood stream for the construction of its own particular protein or proteins.

The proteins include the following groups of compounds: (1) simple proteins, which are broken down during digestion into amino acids and their derivatives and include most of the common protein foods from both animal and plant tissues, such as the albumins, the globulins, and the glutelins; (2) the conjugated proteins, such as nucleoproteins, glycoproteins, phosphoproteins, and hemoglobins, all of which contain a protein molecule in combination with some other substance (thus in the respiratory pigment of the red blood cells, hemoglobin, the protein molecule is united with hematin); (3) the derived proteins, which represent the result of chemical changes in the protein molecule following enzyme action as in digestion, such, for example, as the proteoses and peptones formed in digestion.

Vitamins

The fundamental importance of certain accessory substances in the diet of man and various other animals has been increasingly recognized since 1912 when Hopkins[1] established the basic fact that other organic compounds besides carbohydrates, fats, and proteins were required for an adequate diet. These substances, commonly designated as *vitamins*, comprise a heterogeneous group of carbon compounds. In the earlier periods it was supposed that they constituted a closely related group of essential amino acids, hence the term "vitamine,"

[1] Consult the Appendix: Hopkins.

given at that time (later changed to vitamin), was chosen to indicate that they were "vital amines." The identification and synthesis of various vitamins in the last decade has shown that the original belief was erroneous. It is probable, therefore, that the term vitamin will in time disappear, and the chemical name for each of these essential nutritive substances will be used. In the meantime, for convenience, an alphabetical terminology is used: vitamins A, B, C, D, E, and K.

At all events, adequate amounts of the various chemical compounds which are now grouped together as vitamins are essential to normal animal nutrition. The amounts needed are almost infinitesimal in comparison with the total intake of the body, but supplying these requirements means all the difference between the maintenance of the normal functioning of the body and the gradual development of serious pathological conditions, grouped under the phrase: *nutritive deficiency diseases.*

Vitamins are technically defined as "indispensable organic substances which the organism, lacking the ability to synthesize, must obtain from dietary sources." Three primary characteristics roughly serve to differentiate the vitamins. Thus some are soluble in fats, whereas others are soluble in water; they may be resistant to heat (thermostable) or destroyed by heat (thermolabile); and they may or may not be inactivated by oxygenation. But, on the other hand, the vitamins as a group show certain important characteristics in common. Thus, in performing their various functions in the body, all of the vitamins act as specific compounds, which enter into the chemical reactions, and not as catalysts, as were the enzymes, a fact noted in the following discussion of digestion. Furthermore, it can be said that all the vitamins are highly specific in their activity and amazingly potent. Finally, with the exception of vitamin D, none of them is synthesized in the human body. Brief consideration may now be given to the various vitamins as at present identified.[1]

Vitamin A is a fat soluble substance which is widely distributed in plant tissues, particularly those which contain the yellow pigment *carotene* (carrots, squash, sweet potato, etc.), and is also abundantly stored in various animal fats, such as egg yolk, butter, and cod-liver oil. Animal tissues are able to transform carotene ($C_{30}H_{56}$) from the plant into vitamin A ($C_{20}H_{30}O$). It has not been artificially synthesized. This vitamin is primarily a growth-promoting substance and also has a basic effect upon the epithelial tissues generally.

[1] Highly recommended for presenting a general survey of the latest developments in the vitamin field is the Weston-Levine Vitamin Chart, published and distributed by Dr. R. E. Remington, 280 Calhoun St., Charleston, S.C.

Night blindness, due to a lack of visual purple in the retina, is also associated with vitamin A deficiency and may be relieved by adequate supplies of carotene, from which the essential substances may be synthesized.

Vitamin B is a water-soluble vitamin of highly complex molecular structure. The other vitamins, so far identified, consist of the three elements carbon, hydrogen, and oxygen, but the vitamin B complex also contains nitrogen, sulphur, and chlorine. Vitamin B was the first one of these substances to be discovered. This was due to the

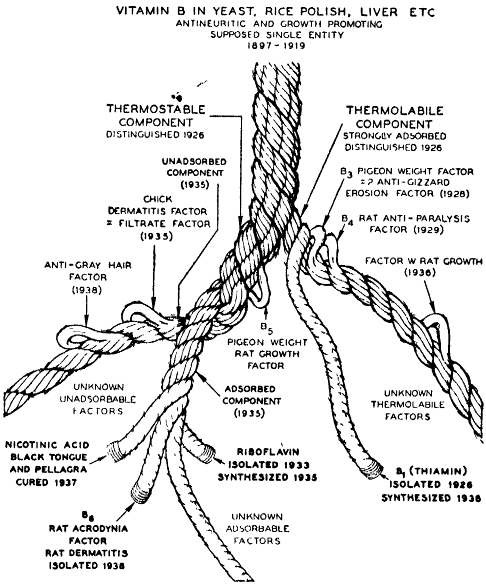


FIG. 35.—Diagram illustrating the components of the vitamin B-complex. Black face lettering indicates components which have been isolated in a pure state; loops in the strands indicate discrepancies in physiological properties of crude extracts. (*Williams and Spies.*)

work of Eijkman, a Dutch investigator, working in Java in the closing years of the last century. He found that the bran coats, or hulls, of cereals contained a substance essential to animal life. In its absence, degeneration of nerve tissue occurred and the development of a paralytic disease known as *beriberi*. Vitamin B also stimulates the general metabolic activities. The vitamin B-complex has since been found to be present, to some extent, in a wide variety of plant tissues as well as in milk, oysters, and lean pork, but its greatest concentration is in bran, the wheat embryo, and yeast. The complexity of the vitamin B-complex and the amount of work yet to be done before a full understanding is reached are well shown by the diagram of

Williams, who succeeded in the artificial synthesis of B_1 (*thiamin chloride*), one of the most important fractions. Another compound present, identified in 1937 as nicotinic acid, is the antipellagra factor. Pellagra has long been known as one of the most serious of the deficiency diseases. (Fig. 35.)

Vitamin C, now known as *ascorbic acid,* is a relatively simple water-soluble compound widely distributed in raw fruits and vegetables, particularly citrus fruits. It is inactivated by the oxygenation that occurs during cooking. It was isolated in 1932 from lemon juice and also from Hungarian red peppers, and its chemical nature determined. A year later, it was artificially synthesized. Ascorbic acid is essential for the intracellular oxidative processes and for the maintenance of normal conditions in the connective tissues of the body, notably bones and teeth. The deficiency disease, known as *scurvy,* results in widespread tissue degeneration.

Vitamin D, now known as *calciferol,* is a fat-soluble compound which is synthesized from fats in the animal body under the influence of direct sunlight on the skin. It is naturally present in egg yolk, salmon, and, particularly in the liver oils of various fish, notably cod and halibut. Calciferol is resistant to chemical action and may be heated or subjected to oxygenation without injury. Irradiation of yeast, milk, and various plant and animal fats with ultraviolet light will produce calciferol. This substance was the first of the vitamins to be produced artificially. This was accomplished in 1927 by irradiation of a plant substance, ergosterol.[1] The specific nutritive deficiency disease due to a lack of calciferol is *rickets,* which is characterized by an upset in the calcium and phosphorus metabolism and a failure to develop normal bone tissue.

Vitamin E, now known as *tocopherol,* is a fat-soluble compound, essential for the maintenance of the normal reproductive activities. It is not affected by heating but is inactivated by oxygenation. So far as known at present, its normal distribution is rather closely restricted in plant tissues. It is abundantly present in the oil obtained from the wheat embryo and also in lettuce and water cress. The normal diversified diet provides adequate supplies of tocopherol. Dietary deficiencies of vitamin E, culminating in sterility, are known only in laboratory animals, notably in rats, that have been kept on an experimental diet. Tocopherol was artificially synthesized in 1938, and so sufficient time has not yet elapsed to obtain the results from later experiments.

[1] Consult the Appendix: Sterols.

Vitamin K belongs to a class of compounds known as the *naptho-quinones*. It is a fat-soluble compound which apparently is essential to blood clotting. In its absence, hemorrhagic conditions develop in the body. The isolation of vitamin K was announced only a few months ago when the compound was obtained from spinach and alfalfa and also from decomposed fish meal. In the latter source, the presence of vitamin K is believed to be due to the chemical activities of decay. Two varieties of vitamin K are recognized under the names K_1 and K_2.

As was recently stated:[1]

> A review of the past decade clearly demonstrates that the discovery of each new vitamin has gone hand in hand with increased purification of ingredients in experimental diets. We do not know how extensive the list of vitamin factors may be when the biochemist can express every component of his experimental diet by indisputable structural formulae. By this time, the term "vitamin" will have long since served its purpose and these substances will be labeled with more specific chemical names such as we now apply to the indispensable amino acids and other constituents of diet.

Digestion and Absorption

The problem confronting the animal organism, in making use of the varied substances brought into the alimentary canal, is to get them into a condition that will permit their absorption by the mucosal cells. It must be remembered that every type of cell, including the absorptive cells of the mucosa, are completely enclosed in a definite membrane of a semipermeable nature. Basically, this means that the openings through the membrane are so limited in size that only very small molecules can pass through them. Such a molecule, for example, is the water molecule formed by the union of two atoms of hydrogen and one atom of oxygen or the molecule of table salt, sodium chloride, composed of one atom of sodium and one atom of chlorine. Substances with molecules the size of the water or salt molecule, or even somewhat larger, pass readily through the membranes of the absorptive cells and so do not have to be changed or digested in the alimentary canal—they are absorbed as they are.

Molecular Size.—Now, the size of a molecule naturally depends upon the number of particles or atoms that are associated to form that particular substance—the more atoms associated the larger the molecule. An idea as to the size of the openings in the membranes of the absorptive cells can be obtained by comparing the size of a molecule of cane sugar, or sucrose, with the monosaccharide molecule. The

[1] Mason, "Science in Progress," p. 156.

chemical formula of glucose, it will be remembered, is $C_6H_{12}O_6$, and that of sucrose is $C_{12}H_{22}O_{11}$. The former is absorbed unchanged by digestion; the latter must undergo digestive action, which results in the formation of two monosaccharide molecules from each molecule of cane sugar. Since the molecules of cane sugar are so small that it would take more than 50 million of them placed side by side to cover an inch in length and they have to be split in half before they can pass through the cell walls, it is apparent that the openings in the semipermeable membranes of the absorptive mucosal cells are very small indeed. (Fig. 36.)

Hydrolysis.—It can be said, then, that digestion is essentially a chemical process by which the too large molecules of the foodstuffs are reduced to molecules of the proper size. Biologists have long been aware of the nature of the digestive processes that accomplish this molecule splitting. It is hydrolysis, a term that means a loosening or change by the action of water. And this is just what happens, for,

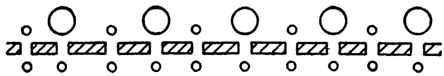


FIG. 36.—Illustrating diffusion through a semipermeable membrane as in the lining of the intestine. The large circles represent sucrose molecules which cannot pass through without digestion; the small circles, water molecules which are small enough to pass through unchanged. (*Seifriz.*)

during digestion, water is added to the complex molecular associations found in the foodstuffs, and the result is the disassociation of the molecules. Hydrolysis is based on enzyme action as described in the following paragraphs. As an example of this essential process, let us again consider the relations between cane sugar (sucrose, $C_{12}H_{22}O_{11}$) and glucose ($C_6H_{12}O_6$). In digestion, the hydrolytic action adds one molecule of water to each molecule of sucrose, thus $C_{12}H_{22}O_{11} + H_2O = C_{12}H_{24}O_{12}$; the latter does not exist as a compound but instead there are two separate molecules of the monsaccharide, or $2C_6H_{12}O_6$. One of these is glucose, but the other has a different arrangement of the associated atoms and is known as *fructose*, but both have the same number of atoms, and both can be absorbed from the digestive tract.[1]

ENZYMES

It is important at this point to consider the essential substances, the digestive enzymes or ferments, that incite the hydrolytic changes associated with digestion, for chemists know very well that merely adding water to either cane sugar or starch will not cause hydrolysis and change the molecular structure of these substances. The answer

[1] Consult the Appendix: Chemical Equations.

is enzyme action. Enzymes, as found in the digestive tract, are complex organic compounds produced by protoplasmic action within the mucosal cells. They are able to cause chemical changes in substances without being changed themselves. Chemists term such substances *catalysts,* and various inorganic substances are known that have this property. Enzymes, however, are organic catalysts of such an intricate molecular pattern that comparatively little is known about their chemical composition, although recent work on the proteolytic enzyme pepsin gives evidence of a protein nature.

Enzymes are highly specific in the substances that they disrupt, but the basic chemical reactions appear to be either hydrolytic in nature in which water is added or taken away from a particular substance, as just noted, or processes that cause an increase or decrease in the amount of oxygen or hydrogen present. Enzymes may be divided into the *extracellular* group which are secreted by the cells and do their work outside the cell body, as in the digestive enzymes which the mucosal cells secrete into the digestive cavity; and the *intracellular* enzymes, which are formed and remain within the cells. Every cell must have its complement of intracellular enzymes, some of which break down, whereas others build up, the materials needed for the continuous chemistry of life.[1]

Digestive Enzymes.—In the earlier discussion of the structure of the nutritive system in man, the localized secretion of enzymes in various regions of the tract has been briefly indicated (page 52). Taking the enzymes now in order of appearance, as they say of the actors on the theater program, further consideration may be given to their functional activities.

Salivary and Gastric Enzymes.—The enzyme ptyalin is secreted by the salivary glands in the mouth and at once begins the digestion of the starch present. Given sufficient time, it will change the starch to maltose, a disaccharide product. Maltose cannot be absorbed but must undergo further enzyme action in the small intestine before the absorbable glucose stage is reached. Ptyalin is effective only in a neutral or slightly alkaline medium, as in the saliva, and is inactivated when the food reaches the stomach where an acid condition obtains.

Pepsin[2] is secreted by the gastric glands in the mucosa of the cardiac portion of the stomach as an inactive substance, pepsinogen. When it comes into contact with the acid gastric juice, it is changed to the active protein-splitting enzyme pepsin, which is effective only in the

[1] The basic importance of enzyme action in all the life processes makes additional consideration advisable. Reference should be made to Chap. XVI.

[2] Consult the Appendix: Beaumont, p. 501.

markedly acid condition of the stomach. The action of pepsin is specific for proteins and results in the formation of the derived protein substances, proteose and peptone, which are incapable of absorption by the gastric mucosa. The first product of protein digestion is a proteose, and most of the proteins remain in this stage during digestion in the stomach, though a slight amount of the proteose reaches the peptone stage. At this point, gastric digestion stops, and the food is passed in the form of liquid chyme into the small intestine for the final stages.

Rennin is also secreted by the gastric glands in an active form. This enzyme has a coagulating action on the milk proteins with the result that the liquid condition is changed into a soft curd, or casein, which can be more readily attacked by the pepsin and other protein enzymes. Since milk is the one food of early life, the importance of rennin is correspondingly great at this period. The same process of the coagulation of milk proteins by rennin is used in the cheese industry.

Pancreatic Enzymes.—Trypsin[1] is secreted by certain cells of the pancreas in an inactive form, trypsinogen. It is activated after reaching the intestine by a coenzyme, enterokinase, secreted by the cells of the small intestine. It is known that the secretion of trypsinogen in the pancreas is incited by a hormone, secretin, thrown into the blood stream by duodenal mucosal cells. The latter are brought into activity by the influence of the chyme from the stomach with its high acidity. Trypsin is one of the most important of all the digestive enzymes. It disrupts the proteoses and peptones present in the chyme, as well as any unchanged protein foodstuffs into the constituent absorbable amino acids. In association with erepsin, noted below, protein digestion is finally completed. The complete pancreatic juice is markedly alkaline, the bile weakly so; together they quickly change the acid chyme into an alkaline fluid, a condition which is essential for the pancreatic enzymes.

Amylase, another important enzyme of the pancreatic juice, is concerned with the digestion of starch, one of the most important of the carbohydrates. Thus it has the same function as ptyalin in the saliva, but it has the opportunity for much more thorough work as the food is under its influence for a much longer period. Comparatively little of the starch present in the food is changed in the mouth, and the amylase converts all that is unchanged into the intermediate disaccharide product, maltose, which is later changed into the simple sugars by the enzyme, maltase, present in the intestinal juice.

[1] It is established that, in addition to trypsin proper, there are two other pancreatic enzymes in the trypsin-complex.

Lipase, the only fat-splitting enzyme of the digestive juices, is the third member of the pancreatic enzyme triad. It is effective on all of the nutritive fats and oils and, through hydrolytic action, splits the fat molecule into a fatty acid and glycerol, both of which pass through the intestinal mucosa into the blood stream. It is recognized that the effective action of lipase in the intestinal tract is greatly aided by the so-called bile salts from the liver, which emulsify the fats. The tiny fat droplets of the fat emulsion can be brought into more effective contact with lipase. Also the bile salts aid in the absorption of the digested fats by forming a temporary, water-soluble compound which readily passes through the cell walls and into the blood stream. The bile salts, thus removed from the intestine in association with the fat products, are later removed from the blood stream by the liver cells and again secreted into the intestine—the so-called circulation of the bile salts.

Intestinal Enzymes.—Erepsin is an important enzyme, or rather a group of enzymes, concerned like trypsin with the final stages of protein digestion. It is a product of the mucosal glands in the duodenum and ileum. It is effective only in the highly alkaline contents of the small intestine, which are largely due, as noted, to the pancreatic juice. The complete action of erepsin and trypsin transforms all the digestible protein material into the constituent amino acids which are absorbed and rapidly transported to the body cells by the blood stream.

Enterokinase is not directly concerned with digestion but acts as a coenzyme with the inactive pancreatic enzyme trypsinogen to form active trypsin, as indicated above (page 64).

Lipase, the fat splitting enzyme, has two sources, being secreted by the duodenal mucosa as well as by the pancreatic cells as just noted.

Maltase, sucrase, and lactase are three important carbohydrate enzymes—all products of the intestinal glands. They are able to split the molecule of the particular disaccharide for which they are adapted into two monosaccharide molecules. As we know, all the disaccharides have the same formula, $C_{12}H_{22}O_{11}$, but the molecular arrangements are different, so that a specific enzyme is necessary for the digestion of each one. The three disaccharides to be digested are maltose which, it will be remembered, is an intermediate product following the action of either ptyalic or intestinal amylase on the starch molecule; sucrose, or cane sugar, which is commonly present in the plant foods; and lactose, or milk sugar, which is the carbohydrate present in milk and a product of the mammary glands of the mammalian female. The enzymes maltase, sucrase, and lactase are so named

because they are specific for the digestion of the three correspondingly named sugars; the end result in all cases is the splitting of the disaccharide molecules into two molecules of a monosaccharide, as indicated above (page 62). The products of carbohydrate digestion pass from the stomach to the liver where, by a reverse process involving the removal of water, the glucose molecules may be changed back by the hepatic cells into still another disaccharide, glycogen or animal starch, which is temporarily stored in the liver until needed for fuel by the body tissues. When this need arises, enzymes in the liver cells hydrolyze the glycogen and so form glucose again, which is secreted into the blood stream and supplied to the body cells for their energy requirements.

Synthesizing Enzymes.—It may be well at this point to link up the enzyme actions associated with the digestive processes with those in which the large molecular units are reestablished within the living cellular units. This is the process of assimilation, that is, the actual incorporation of the new materials into the life stream. It can be said in a word that the intracellular synthesis is exactly the reverse of digestion, water being removed as the molecules are joined to form the more complex compounds. In either case specific enzymes are responsible. Those concerned with digestion are able to add water and thus split the large, complex molecules, of the foodstuffs whereas the synthesizing enzymes are able to remove water and join the molecules together in more complicated association.

Obviously, the disintegrative enzyme actions essential to digestion are not to be regarded as of more importance than the synthetic reactions by which the digested materials—glucose, fats, and amino acids, together with the inorganic substances—are constantly being synthesized within each cell to form the specific materials essential for upkeep, growth, and fuel. No matter what specialized functions the various types of cell may have in the body, each one must be able to construct its own type of protoplasm by means of the particular intracellular synthesizing enzymes that are characteristic of it. Thus even the mucosal cells of the alimentary tract, which secrete digestive enzymes for extracellular use, are at the same time maintaining and utilizing their own intracellular equipment of enzymes for synthesizing and disrupting organic cellular compounds as occasion demands.

PHOTOSYNTHESIS

In connection with the synthetic enzyme actions, it will be profitable to reexamine in some detail the photosynthetic processes in green plants that were briefly indicated in the opening chapter (page

11). Photosynthesis is based upon the unique ability of chlorophyll[1] to utilize the energy of sunlight for synthesizing carbon compounds of such a nature that they can be utilized as food by living organisms. The substances taken into the plant cell for the photosynthetic reactions consist of carbon dioxide (CO_2), which is a gas composed of the

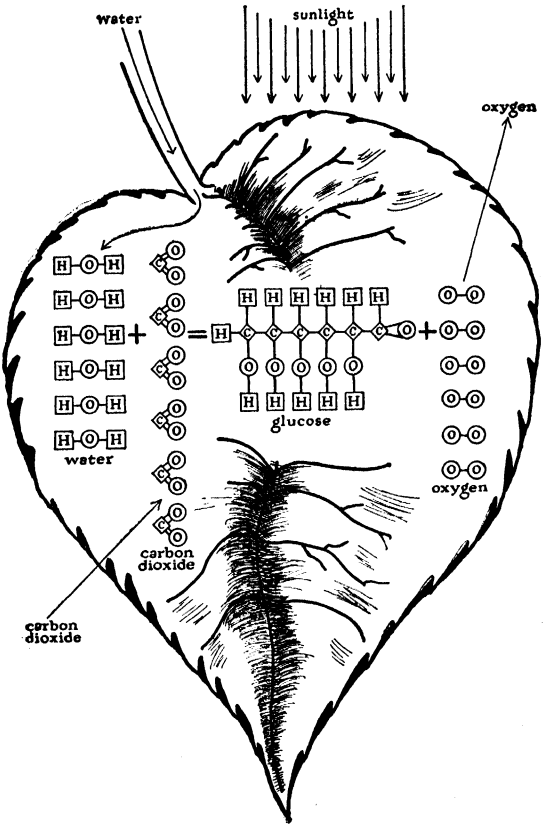


FIG. 37.—Diagram illustrating the process of food formation, or photosynthesis in the green leaf as described on pages 66–68. (*Smith, "Exploring Biology," Harcourt, Brace & Company, Inc.*)

elements carbon (C) and oxygen (O) combined in the proportion of one carbon atom to two oxygen atoms, and water (H_2O), which is composed of two atoms of hydrogen and one atom of oxygen. Essentially, chlorophyll is able to make use of the radiant energy of the sun to separate the carbon from the oxygen in the carbon dioxide molecules and to combine the carbon thus secured with the hydrogen and oxygen of the water to form a carbohydrate, a simple sugar, glucose, having

[1] Consult the Appendix: Chlorophyll.

the chemical formula $C_6H_{12}O_6$, which is the first food product of photosynthesis. At least one synthetic enzyme, chlorophyllase, is associated with the chlorophyll, but the exact relations are obscure. At all events the chlorophyll-enzyme complex is responsible for the union of the carbon dioxide and water since it is not possible to get the reaction in the laboratory in the presence of sunlight alone. (Fig. 37.)

In photosynthesis, six molecules of carbon dioxide are combined with six molecules of water to form one molecule of sugar. When this is done, six molecules of oxygen remain. The essential facts of photosynthesis, as the chemist sees them, are expressed in the following chemical equation:

$$6CO_2 + 6H_2O = C_6H_{12}O_6 + 6O_2.$$

The oxygen separated from the carbon dioxide molecule and not utilized in photosynthesis passes off into the atmosphere as free oxygen. Oxygen is an active element and tends to combine very quickly with other elements when it comes into contact with them. Practically the only available supply of free oxygen for respiration is that liberated through photosynthesis. Thus it is apparent that living organisms depend upon photosynthesis not only for their food but also for the essential oxygen which alone makes it possible for the complex foods to be utilized. (Fig. 38.)

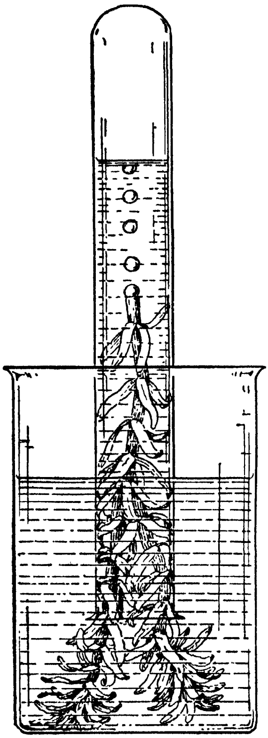


FIG. 38.—Diagram of an experiment illustrating release of oxygen during photosynthesis in *Elodea*, a common water plant. The bubbles are passing up from the cut end of the stem and displacing water in the test tube. (*Haupt.*)

The basic food compound formed by photosynthesis, as just noted, is a simple sugar, *glucose*. It is present in animal cells as well as plant cells. Thus in the human organism it is glucose that is finally formed from the digestion of starch and all types of carbohydrate. And glucose is the primary carbohydrate carried in the blood stream to the cells of the body where it is oxidized as necessary, thus releasing the energy previously stored in photosynthesis. Glucose, having been formed in the green plant cell, (1) may be oxidized at once to secure energy; or (2) it may be changed to other more complex carbohydrates and stored for later use; or (3) the proportion of oxygen present in

either the sugar or the starch may be decreased, and thereby the substance changed from a carbohydrate to a fat which may also be stored for later utilization as necessary; or, finally, (4) the plant cells have the power to add additional elements, essential to the living tissues, to the carbohydrate molecule thus forming the proteins which, in turn, are built into protoplasm.

It has just been noted that various possibilities await the glucose after being synthesized. Let us first consider its transformation into other carbohydrates. As the first step, the monosaccharide may be changed by the plant cells into cane sugar, that is, the disaccharide, sucrose ($C_{12}H_{22}O_{11}$). Synthesizing plant enzymes accomplish this by the removal of one molecule of water from each two molecules of glucose. Thus: $2C_6H_{12}O_6 - H_2O = C_{12}H_{22}O_{11}$. When the cane sugar is taken into the animal digestive tract, it will be acted upon by the specific digestive enzyme, sucrase; a molecule of water is added to each sucrose molecule, which brings back the original condition with two molecules of glucose (page 62).

But the glucose of the green plant cell may be changed for storage into a still higher type of carbohydrate, the polysaccharides, notably cellulose and starch. When a polysaccharide is formed, the synthetic enzyme action results in the removal of one molecule of water from each molecule of glucose. Thus: $C_6H_{12}O_6 - H_2O = C_6H_{10}O_5$. But a polysaccharide consists of many of these anhydrous glucose residues joined together, and so the formula is written $(C_6H_{10}O_5)_x$. Furthermore, the ultramicroscopic starch molecules may be combined to form starch grains which are of microscopic visibility. The starch grains of a particular species are always of characteristic size and shape.[1]

From the standpoint of plant structure, the most important carbohydrate is the polysaccharide, cellulose. This carbohydrate has the same composition as starch; that is, it consists of associated glucose residues, $(C_6H_{10}O_5)_x$, but the arrangement of the atoms is different and results in a much more resistant substance, which is utilized as a plant-building material. Plant cells are characterized by prominent cellulose cell walls which are formed as a secretion around the living protoplasm. As the cells get older, more and more cellulose accumulates, and so this material largely forms the structural basis of plant tissues. Woody tissue, for example, is predominantly cellulose and associated compounds. Plant cells, as a rule, are not long-lived, but, before the protoplasmic activities cease, considerable cellulose is laid down, and these cellulose-encased cellular units remain as the permanent structural units of the woody tissues. Consideration of the

[1] Consult the Appendix: Starch.

many uses that man finds for cellulose, for example, in the building, textile, and chemical industries, makes evident the commercial importance of this most abundant of all carbohydrates. The use of cellulose as a foodstuff, however, is limited by the fact that the digestive enzymes of many organisms, including man, are not able to digest this resistant material.[1]

In cellulose, the linkage of the glucose residues is so rigid that the digestive action of the human tract is not strong enough to separate them, though cellulose digestion is accomplished by the herbivorous animals. In the woody tissue of trees, which is also largely cellulose, the molecules are even more strongly attached to each other so that woody tissue cannot be utilized as food even by the plant eaters. Certain wood-eating insects, the termites, manage to utilize woody tissue, but they do it by maintaining in their digestive tract a tremendous staff of one-celled animals, the flagellates, which possess enzymes sufficiently powerful to produce hydrolysis of woody tissue. (Figs. 231, 232.)

The essentials of the story are the same in the fats and proteins as in the carbohydrates. Fats are built up either in the plant cells or in the animal cells by a combination of fatty acids and glycerol, and water is removed during the synthesis. In the digestion of a fat the restoration of the water by an enzyme action splits it into the original fatty acids and glycerol. Finally, plant cells have the power to combine other essential elements of the protoplasmic assemblage with the carbohydrates produced during photosynthesis and thus to form the proteins which are, in turn, built into the protoplasm. It is not certainly known that protein formation is directly associated with the photosynthetic processes that produce the carbohydrates. Evidence exists that protein formation may occur in any plant tissue and in the absence of light, but, nevertheless, the chlorophyll-bearing cells in the leaves appear to be the most active centers of protein formation.

Proteins are not formed directly from the carbohydrate molecule, but the less complex amino acids are first built up, the simplest of which contain only nitrogen in addition to the carbon, hydrogen, and oxygen. Altogether, around two dozen amino acids are known, but from these relatively few "amino acid building stones" it is possible to construct an almost infinite number of proteins in the cells of the plant and animal tissues. Thus from 20 known amino acids, it has been calculated that at least 2,432,902,008,176,640,000 different compounds could be formed without even varying the proportion of the

[1] Consult the Appendix: Cellulose.

different amino acids in a single protein.[1] Furthermore, it must be emphasized that protoplasm, as the "vehicle of vital manifestations," consists not of one but of various proteins, which, in turn, are associated with representatives of the carbohydrates and fats, the entire protoplasmic setup being so extraordinarily complicated and capable of such great variation as to make possible the almost infinite variety of organisms present in the living world today.

In the digestion of proteins, the proteolytic enzymes (pepsin, trypsin, erepsin) are able to bring about the introduction of water and thereby split the protein molecules step by step into the amino acids (page 57). Thus the complicated chemical processes associated with the digestion of the proteins finally yield amino acids, and the latter are resynthesized into proteins by each cell individually.

Synthesis of protein and other substances in the cell from the materials rigidly selected from the environment results in the formation of proteins that are "custom-tailored" to supply the needs of each individual cell and not necessarily a duplication of the proteins in the foodstuffs originally taken into the digestive tract. The various plant and animal proteins that are eaten represent the synthetic activities of the cells of some other plant or animal organism. All proteins built into the living protoplasm are, of course, within the cells—life exists only within the cells—but less complex proteins are found in the blood plasma, the ground substance of the connective tissues, etc. These proteins outside the cells represent cell secretions, that is, materials that have been manufactured within the cells and then secreted.

In summarizing, the essentials of the nutritive processes can be stated very simply; the battery of enzymes present in the alimentary tract is able to hydrolyze the specific foodstuffs for which they are adapted—the end result being that all suitable types of carbohydrates are finally converted into the simple sugars, that all the fats are converted into fatty acids and glycerol, and that all the proteins are changed into amino acids. These constitute the organic substances that are absorbed from the alimentary tract and transported to the body cells and from which the cells make their own individual selections for intracellular reactions, as noted above. Added to the absorbed nutrients are the soluble vitamins and simple inorganic substances, notably water and table salt, together with a wide assortment of mineral elements combined in some way with the organic substances; all of which are apparently unchanged by the digestive actions.

[1] The possible number of proteins that can be formed by combinations of amino acids may perhaps be visualized by considering the number of words that can be formed from the 26 letters of the alphabet.

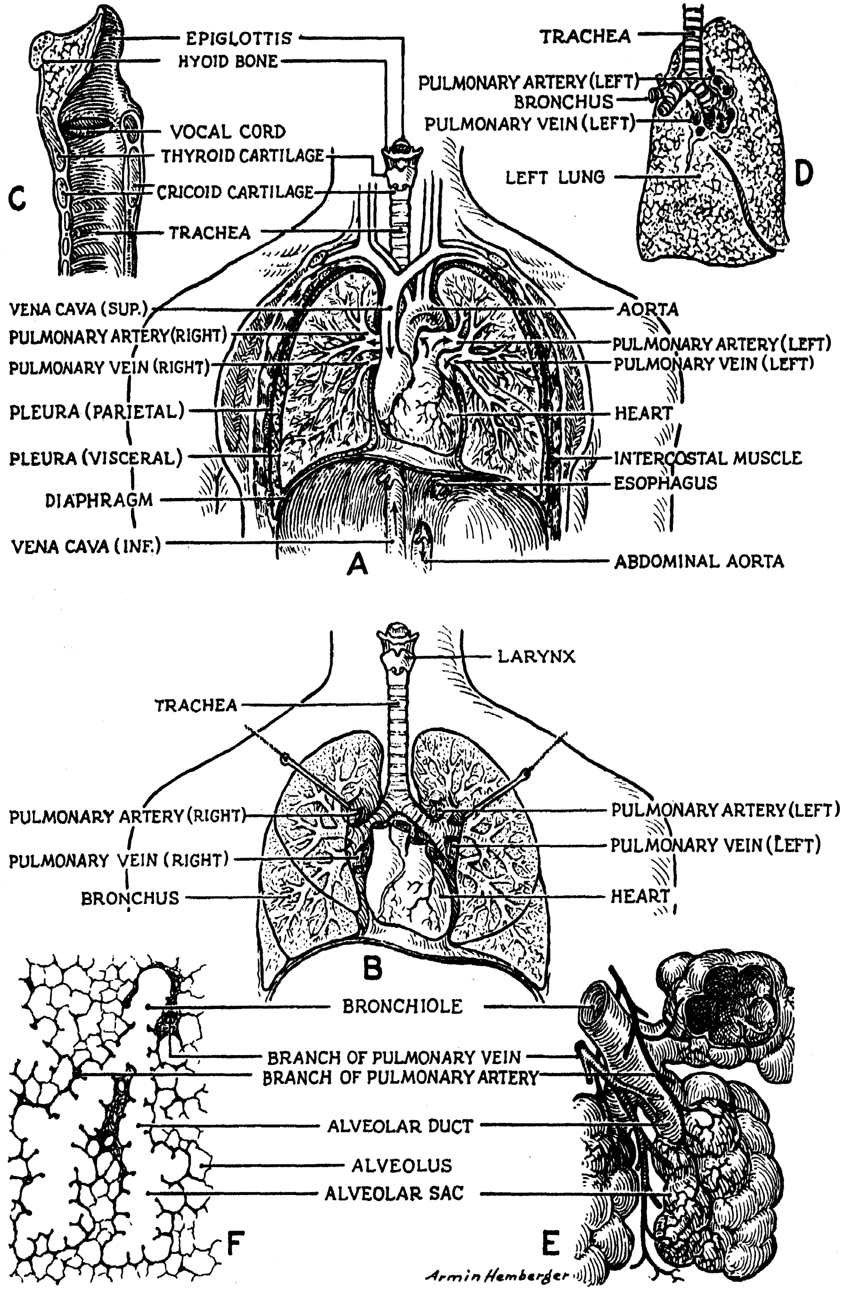


PLATE IV.—Human lungs and associated structures. *A*, relationship between lungs and vascular system; *B*, relationship between lungs and trachea; *C*, longitudinal section of anterior end of trachea; *D*, left lung and bronchi; *E*, infundibula; *F*, microscopic section of lung tissue.

CHAPTER IV

THE BIOLOGY OF RESPIRATION

We have seen that the elements essential to the living organism are assembled and combined in the green plant cells and that, through the formation of organic compounds from inorganic materials, the radiant energy of the sun is made available for the metabolic activities following intracellular oxidation—the process of respiration. The changes associated with digestion, considered in the previous chapter, do not disturb the energy relations of the foodstuffs; the nutrient materials are merely changed so that they can be absorbed and assimilated by the living cells. Respiration, by which the potential energy of the stored compounds is transformed into active, or kinetic, energy, occurs in each cell. Required for this process is free oxygen which combines, under the influence of intracellular enzymes, with the accumulated materials and disrupts them through complex oxidative processes.

Certain microscopic fungi, the anaerobic bacteria, do not utilize the free oxygen of the air but secure this element by breaking down suitable oxygen-containing compounds through enzyme action. The overwhelming majority of plants and animals, however, are aerobic; that is, they must have free oxygen which they secure either from the air or from fresh or salt water, all of which normally contain a sufficient amount of oxygen uncombined with other substances. The oxygen in solution can easily be driven out by boiling the water. Then no aerobic organism could live in it, for none of them are able to destroy the water molecules and thus secure oxygen.

In the microscopic unicellular forms of life, the interchanges of gases associated with respiration appear to be comparatively simple. The organism finds sufficient free oxygen dissolved in the surrounding liquid environment which it utilizes as needed and releases the subsequently formed carbon dioxide in the same fashion. In the highly developed multicellular forms of life, the basic processes associated with respiration are identical with those of the unicellular types of life, but the mechanism necessary to get the oxygen into the body and to convey it to each of the constituent cells greatly obscures the respiratory picture. In fact, respiration in man is commonly thought

of as being identical with the process of breathing. The latter function, however, is merely a method of getting the oxygen into the body. Breathing is essential to respiration, but it is not respiration. Some authorities speak of external respiration, meaning the act of breathing as distinguished from internal respiration which is used to indicate the cellular intake and utilization of oxygen, the basic feature of respiration. Physiologists do not know just how respiration is accomplished in the cell; they know only the start (oxygen taken in), and the result (energy released), with the elimination of the end products. Accordingly this chapter is from necessity mainly a description of the structural and functional features of the respiratory mechanism in man by which oxygen is secured and the resulting compounds, which are of no use to the cell, excreted.

STRUCTURAL FEATURES ASSOCIATED WITH RESPIRATION

In the aquatic animals, a variety of structures are utilized to secure the necessary oxygen from the environment. In all of these organisms,

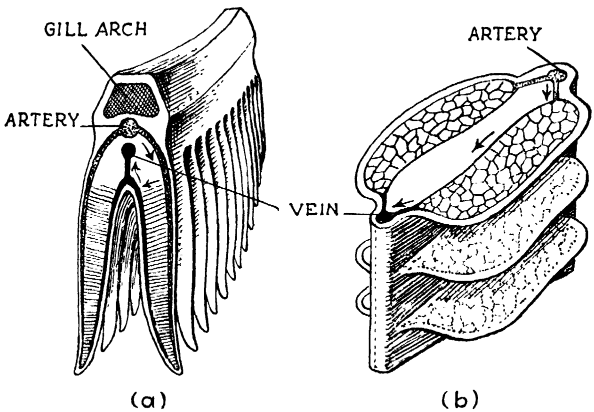


FIG. 39.—*a*, diagram illustrating the general gill structure of a fish; *b*, portion of the gill, highly magnified. Arrows show the course of the blood stream in its passage through the gill tissues. (*Goldschmidt, "Ascaris," Prentice-Hall, Inc.*)

however, the essential element in the oxygen-collecting equipment proves to be a tissue abundantly supplied with blood vessels and covered on the surface in contact with water by specialized epithelial cells, which are able to take up the oxygen from the water and to turn it over to the special cells in the blood stream for transportation to the cells of the body. Such, essentially, are the gills of fish and similar organs in other water-living forms. (Fig. 39.)

In the air-breathing animals, the oxygen-collecting apparatus is of the same basic design as in the water-living animals. Again there is

a special tissue abundantly supplied with blood vessels and covered on the outer surface with specialized epithelial cells, but the latter, in the air-breathers, are adapted to take oxygen from the air instead of from water. The reason why a fish cannot live out of water and a man cannot live in water rests directly upon the inability of the epithelial cells of these organisms to extract oxygen from the strange environment in which they suddenly find themselves. In man and air-breathers generally, the lungs serve as the oxygen-collecting apparatus. But in one very large and important animal group, the insects, air tubes are not concentrated to form lungs but ramify all through the body tissues and open to the exterior on the sides of the body. Air is carried to the body cells through these tracheal tubes, and the body cells pick up the oxygen directly from them so that an intermediate vascular system is not needed for its conveyance. (Fig. 40.)

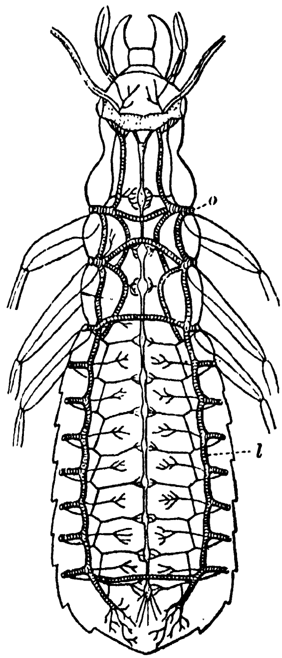


FIG. 40.—Diagram illustrating the tracheae in an insect which carry air directly to the tissues. *l*, longitudinal trachea; *o*, external opening (spiracle.) (*Goldschmidt*, "*Ascaris*," *Prentice-Hall, Inc.*)

The Lungs and Trachea.—In the simplest condition, found in the more primitive air-breathing vertebrates such as the adult frog, the lungs consist of a pair of small distensible sacs. Each of these lung sacs is connected with an air-conducting tube, the trachea, which opens into a common laryngotracheal cavity. The latter lies underneath the floor of the mouth, near the posterior end, and opens into the mouth cavity through an elevated circular glottis at the base of the tongue. The walls of this comparatively simple type of lung are more or less contractile and highly vascularized. The lining of the lung is thrown into folds that project in the cavity to such an extent that numerous tiny, partially closed air cavities are formed. Air passing through the glottis reaches the lungs and comes into contact with the functional respiratory cells that line it. These absorb the free oxygen from the air and turn it over to the blood stream and at the same time remove the carbon dioxide for excretion. Even more important than the lungs in the respiratory activities of the frog is the skin, for the latter is responsible for the greater proportion of the respiratory exchange. Through living in the water, the surface of the frog's skin is constantly

wet. In this condition, the skin, with its abundant supply of blood vessels, readily permits the inflow of oxygen and release of carbon dioxide. The result is that the blood returning to the body-tissues from the skin is as well oxygenated as is that from the lungs. The capacity of the frog's lungs is not sufficient to maintain adequate oxygenation of the blood. Accordingly the animal will die if the skin becomes dry, thereby preventing the normal respiratory interchange. (Fig. 41.)

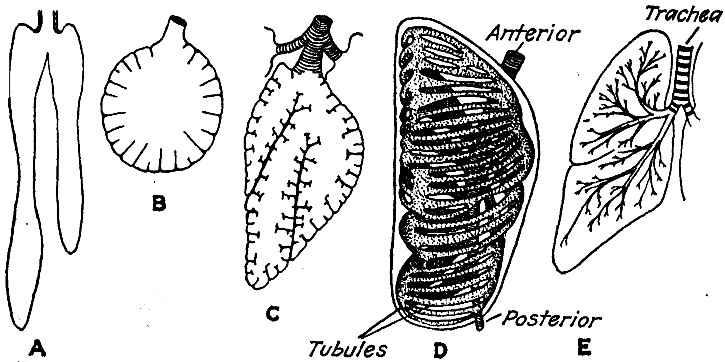


Fig. 41.—Diagrams illustrating lung structure in various vertebrates. The higher types are characterized by an increasing amount of lung surface exposed to the air. *A*, necturus, no alveoli; *B*, frog; *C*, lizard; *D*, bird; *E*, mammal, with branching bronchi. (*Wolcott, after Locy and Larsell.*)

THE RESPIRATORY SYSTEM OF MAN

In the higher vertebrate animals such as man, which are not adapted for aquatic life, the skin has almost entirely lost its respiratory function, and a corresponding development of the lungs has necessarily occurred, since they must bear the entire burden of the respiratory exchange with the environment. The position of the lungs in the thoracic cavity has already been noted, as has also that of the trachea, or windpipe, connecting them to the throat. Both the nasal passages and the mouth may be used for the intake and release of the respiratory gases. It is apparent that breathing through the nose is the correct method, for the epithelium lining the large areas of the nasal cavities contain mucus-secreting cells. The secretion from these cells covers the nasal epithelium and aids in removing dust particles from the incoming air stream. Also the temperature of the incoming air is rapidly brought to body temperature as it moves through the nasal passages, which thus serve as an efficient air-conditioning apparatus. Unfortunately, the nasal passages are subject to partial or complete stoppage following head infections, and then the mouth opening must be utilized to maintain the constant air supply.

Whether taken in through the nose or mouth, the air current passes swiftly to the common throat region, enters the trachea through the upraised epiglottis, finds its way through the glottis, and reaches the lungs. (Figs. 30, 42.)

The trachea is a cartilaginous tube with rings of heavier material encircling the wall at regular intervals so that it does not collapse. Considerable areas of the trachea are lined with ciliated epithelial cells, the effective beats of which are directed away from the lungs. The ciliary action is effective in removing foreign materials from the respiratory tract. The anterior end of the trachea is modified to form a complicated box-like larynx, or Adam's apple. The epiglottis is attached anterior to the larynx, with the glottis, through which the air passes in and out of the trachea, lying just below. The larynx is essentially an apparatus for the production of sound and has nothing to do with respiration. It is so placed and constructed that advantage can be taken of the outgoing air currents to initiate vibrations of the taut vocal cords which form the boundaries of the glottis. Sounds of varying pitch are thus produced. The use of the larynx in speech is considered in more detail below.

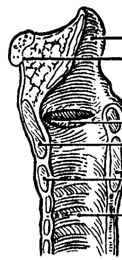


FIG. 42.—Longitudinal section through the anterior end of the human trachea.

The Lungs.—Shortly before reaching the lungs, the trachea divides to form right and left branches, the bronchi, each of which enters the lung on its side and then proceeds to form smaller and smaller subdivisions, the bronchioles. The bronchioles terminate in tiny, enclosed air-sac structures, shaped somewhat like a bunch of grapes, the infundibula, which approximate $\frac{1}{30}$ in. in diameter. The inner lining of the infundibula is arranged in such a way that incredible numbers of the basic units for respiratory exchange, the alveoli, are formed. The alveoli are essentially closed cavities or air sacs, each one of which has a direct connection to the trachea through the attached bronchiole; the latter in turn communicating with the bronchi, trachea, and then the exterior. The walls of the alveoli contain supporting tissues, particularly elastic tissue which permits considerable

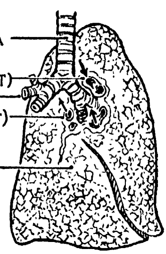


FIG. 43.—Illustrating the general structure of the human lung and its connection with the trachea, as seen from the ventral surface.

expansion. But functionally of greatest importance is the respiratory epithelial tissue which forms a lining, one cell thick, throughout every alveolus. It permits the exchange of oxygen and carbon dioxide between the contained alveolar air and the blood stream flowing through the tiny vessels that abundantly permeate the alveolar walls just beneath the lining epithelium. Thus air passing through the trachea, bronchi, bronchioles, and infundibula finally reaches the alveoli and here comes into contact with the moist lining epithelium through which the respiratory exchange takes place. Since the lungs develop in the early embryo as outgrowths from the primitive endodermal-lined gut, it is clear that the functional respiratory epithelium lining the lungs is of endodermal origin just as is the mucosa of the alimentary tract. (Figs. 43, 44.)

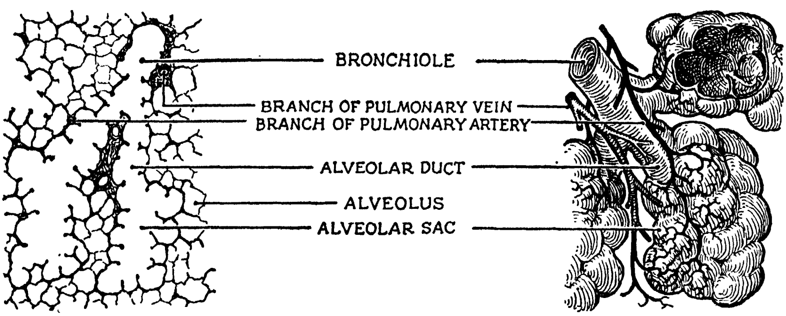


FIG. 44.—Illustrating the microscopic structure of lung tissue. Right, termination of the bronchioles to form alveolar sacs which are grouped as infundibula; left, section of lung tissue as seen under the microscope.

The lungs are covered with, and the thorax is lined by, the pleura, a thin epithelial membrane developed from the mesoderm. It is of the same nature as the peritoneal lining of the abdominal cavity, which, it will be remembered, is reflected over the viscera and forms the mesenteries supporting the intestines. When the lungs are fully inflated, their pleural covering is in contact with the pleural lining of the thoracic cavity; but under conditions of partial inflation, a space, the pleural cavity, lies between the two layers. Infection of the pleural membranes, which is not uncommon following pneumonia, is known as *pleurisy*. (Plate IV*A*, page 72.)

The respiratory epithelium, lining the innumerable air sacs of the lungs, is a very thin layer, but it covers a great surface area. It has been computed that the total area of the lung cavities is some sixty times that of the body surface. Also the total air capacity of the lungs is far in excess of the actual needs of the body. The average person when resting does not use more than 5 per cent of the total lung capac-

ity. Under conditions of severe muscular activity, the gaseous exchange through the lungs is greatly increased, but, even so, the normal lung capacity is always more than ample. Many persons are living active lives whose lung capacity has been reduced by half as the result of the destruction of lung tissue following tuberculosis. (Fig. 44.)

Lung Capacity.—The vital capacity of the lungs is the maximum amount of air that can be exhaled following the maximum inspiration, and it amounts to about 240 cu. in., or 3,700 cc., in the average medium-sized person. Residual air is the air remaining in the lungs that cannot be expelled. It amounts to another 1,000 or 1,200 cc., so that the maximum air capacity of the lungs is not far from 5,000 cc. But these maximum figures are possibly not so important as the ones associated with normal breathing. The latter condition involves the movement in or out of the lungs of approximately 500 cc. of tidal air. An additional 1,600 cc. of complemental air can be drawn into the lungs, or an additional 1,600 cc. of supplemental air can be expelled if desired. Tidal air plus complemental air plus supplemental air totals about 3,700 cc., which is the vital capacity as defined above. And the vital capacity plus the residual air makes the maximum capacity of the lungs about 4,800 to 5,000 cc., as stated earlier.

Respiratory Gases.—It is clear from the data just given that the 500 cc. of tidal air, which is all that is moved in ordinary breathing, is less than one-seventh of the vital capacity. The supplemental and residual air are essentially stationary. Furthermore, of the 500 cc. of tidal air brought into the lungs at each normal inspiration, only about 350 cc. of new air enters, because of the fact that some 150 cc. of tidal air was in the bronchi, trachea, and throat when the inspiration stopped, and this old air, therefore, goes back into the lungs when the tide turns. The point to emphasize in all this is that relatively little air is brought into the lungs from the outside at each breath; a mixture of old air and new air is always present; and accordingly no radical change in the alveolar air takes place when inspiration occurs. The amount of air taken in at each inspiration is sufficient to keep the oxygen and carbon dioxide content at the proper levels so that the blood is always adequately aerated. The oxygen–carbon dioxide

Air	Nitrogen, per cent	Oxygen, per cent	Carbon dioxide, per cent
Inspired	79	20.96	0.04
Expired	79	16.62	4.38

relationships are shown by the table on page 79 giving the gaseous content of the inspired and expired air.

Thus it is shown that the expired air drawn from the lungs contains a much higher percentage of oxygen than of carbon dioxide—in fact, nearly four times as much. The expired air contains certain other substances picked up in lungs in addition to the carbon dioxide, notably water vapor, which amounts to some 250 cc. per day (½ pt.), and a slight amount of organic excretions. And, of course, the temperature of the air leaving the body is that of the body and not that of the atmosphere (page 127).

An important factor in maintaining an adequate supply of oxygen appears to be the relative amount of carbon dioxide present. Thus, if air is inhaled that contains around 5 per cent of carbon dioxide instead of the normal 0.04 per cent, the breathing movements are markedly increased as the percentage of carbon dioxide gradually increases in the lungs. On the other hand, if one voluntarily resorts to forced, heavy breathing of air containing the normal amounts of oxygen and carbon dioxide, the percentage of carbon dioxide in the alveolar air will soon be decreased. In correspondence with the decrease in the carbon dioxide, the respiratory movements will be involuntarily reduced or suspended entirely—the condition of acapnia—until the percentage of carbon dioxide again reaches the normal level.

In addition to the nitrogen, oxygen, and carbon dioxide given in the foregoing table, atmospheric air contains about 1 per cent of a mixture of inert gases, notably argon and neon. Adding this to the nitrogen, which is also inert and goes in and out of the lungs with essentially no change in volume, it is found that 79 per cent, or nearly four-fifths, of all the gases in the air we breathe has no part in the chemical activities of respiration. The inert gases do, however, serve to dilute the oxygen, and this function is important, since pure oxygen is a destructive agent to the tissues.

Normal breathing occurs about every 4 seconds, or 15 times per minute, but the rate is subject to considerable variation in different persons and in the same person under different conditions. As noted, 500 cc. of tidal air is inhaled at each breath so that each minute 7,500 cc., or 7.5 liters, nearly 8 qt., of air is taken into the lungs and the same amount removed. However, only 5.4 liters of this is new air, as noted above. It is commonly stated that every minute of the day, under normal conditions, some 250 cc. of oxygen is removed from the inspired air, and slightly less than this amount of carbon dioxide added to the air leaving the lungs. The oxygen acquired in this fashion is the amount required by the cells of the body for the essential metabolic

processes. Computing this on the 24-hour basis, the oxygen need is found to be 360 liters, or between 12 and 13 cu. ft.

BREATHING

Respiratory Movements.—The movements associated with breathing result from the coordinated control by the nervous system of a number of diverse muscular elements, situated in the walls and in the floor of the chest cavity, which exert their pull upon the bony ribs. The ribs are attached dorsally to the spinal column in a manner that permits of considerable freedom of movement. Ventrally, the anterior 10 pairs of ribs are attached to the unjointed cartilaginous sternum, whereas the last two pairs are attached only to the spinal column. The curvature of the ribs and their mode of attachment are such that when the intercostal muscles lying between the ribs contract, the ribs are drawn up (toward the head) and out (toward the ventral body wall). This results in markedly increasing the size of the chest cavity in which the lungs are situated. The size of the chest may also be increased by the contraction of the muscle fibers in the diaphragm, which forms the floor of the thorax. In the relaxed condition, the diaphragm is somewhat U-shaped, with the bottom of the U turned upwards toward the lungs. When contraction occurs, the U is greatly flattened, and thus the diaphragm is pulled posteriorly (that is, away from the lungs and against the abdominal organs), and this, of course, results in an enlargement of the chest cavity. (Fig. 45; Plate IV*A*, page 72.)

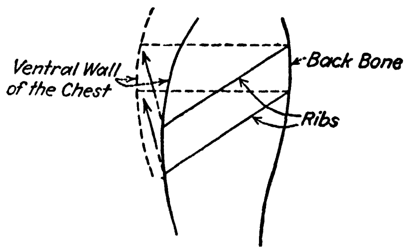


FIG. 45.—Diagram illustrating enlargement of the chest during inspiration by movements of the ribs. (*Watkeys, Daggs.*)

Those who have not studied the matter, generally have the impression that air is sucked into the lungs and that the chest expands to accommodate the air that has been taken in. This is getting the cart before the horse because what happens when air is inhaled is that the size of the chest is first increased by the contractions of the intercostal and diaphragm muscles as described in the preceding paragraph. The walls of the chest cavity are airtight; and when the cavity is enlarged and a partial vacuum thereby created, the outside air, impelled by the atmospheric pressure of 15 lb. per square inch, rushes into the region of lowered pressure, and the lungs are expanded to fill the additional space. This action is nicely demonstrated by a model in which a glass bell jar is used to illustrate the chest wall. The open end of the bell jar

is closed by a sheet of flexible rubber which represents the diaphragm. The lungs and windpipe are represented in the model by a rubber sack tied to the end of a glass tube. The rubber lungs and a portion of the glass windpipe are inserted through the top of the bell jar and sealed airtight. Now if the air capacity of the bell jar is increased by exerting a pull on the rubber diaphragm, air will rush through the open tube into the "rubber lungs," and they will expand in accordance with the lowered pressure in the bell jar. (Fig. 46.)

Accordingly, it is evident that the intake of air into the lungs is essentially dependent upon rhythmic muscular contractions which

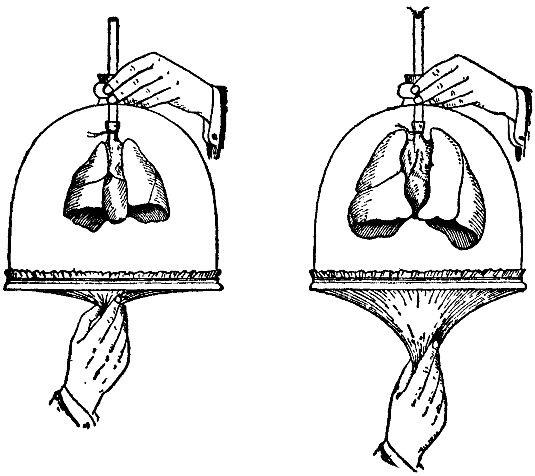


Fig. 46.—Diagram illustrating the inflation of the lungs as described on page 81. In this experiment a pair of mammalian lungs have been used, but the use of a rubber sack, such as a toy balloon, is simpler. (*Woodruff, after Tigerstedt; redrawn.*)

result in the enlargement of the chest cavity. Less evident is the muscular action in expiration, which appears to be more of a passive process associated with muscular relaxation and the natural tendency of the expanded alveoli in the lungs to return to normal size. In the lowering of the ribs, the gravity pull undoubtedly has some influence. The elevation of the diaphragm that occurs in expiration is associated both with the relaxation of the muscle fibers and also with a contraction of another set of muscles in the abdominal wall. The contraction of the latter compresses the abdominal viscera and pushes them upward against the under surface of the diaphragm and thus accelerates its return to the original U-shape. In heavy breathing following increased physical exertion, both the inspiration and expiration are aided by the contraction of additional muscles in the ribs and body wall that come into play when necessary.

Certain common variations of ordinary breathing are noteworthy. One of these is coughing, which is a violent expiratory effort resulting from various types of respiratory irritation. The cough is preceded by a heavy inspiration. The glottis is then closed; the expiratory muscles, chiefly in the abdominal wall, contract and force the air through the glottis and out the mouth. Sneezing is essentially the same as coughing, except that the passage through the mouth is closed by the soft palate, and the outrushing air is forced to escape through the nasal passages. Another all too common respiratory irregularity is the hiccough. This is due to the closing of the glottis during a sudden inspiration. The trouble apparently originates in the diaphragm which contracts irregularly and thus brings on the sudden inspiration. The incoming air, hitting the closed glottis, causes the characteristic sound.

Control of Breathing.—Breathing is normally under involuntary control. It keeps going whether we think about it or not. But if it is desired, breathing can be increased, reduced, or even temporarily stopped. Thus voluntary control is possible within certain limits. However, when a certain stage has been reached, as in holding one's breath, the involuntary mechanism again takes control, and breathing is resumed. The respiratory center, which normally governs the rhythmic muscular contractions associated with breathing, is situated in a portion of the hindbrain, known as the *medulla*. The nature of the respiratory center itself is in doubt. Some hold that it is entirely automatic in its action, a "robot," so to speak, influenced when necessary by changing conditions but continuously forming and discharging the impulses that pass over the nerve fibers and cause the muscular movements. On the other hand, the respiratory center may be merely a reflex center that simply relays impulses received from higher centers to the respiratory muscles. At any rate, it is certain that the condition of the blood, particularly the carbon dioxide content, as well as various external influences are effective in modifying the impulses from the respiratory center.

The determining factor in the behavior of the respiratory center appears to be the amount of carbon dioxide released into the blood by the body tissues, and this amount, of course, is in direct ratio to the cellular activities, particularly those associated with movement. The carbon dioxide picked up by the blood stream is not carried as such, for it immediately combines with the water in the plasma to form carbonic acid, thus: $CO_2 + H_2O = CH_2O_3$. Carbonic acid tends to lower the normal alkalinity of the blood plasma, and this condition affects the respiratory center. The latter, in turn, stimulates the

respiratory muscles to greater activity in an endeavor to keep the blood gases at normal levels by increasing the rate of breathing. On the other hand, if the alkalinity of the blood tends to rise above normal as the result of superaeration of the blood in the lungs, impulses flowing to the muscles from the respiratory center will be lessened, and breathing activities will be greated reduced or even entirely suspended until the normal levels are attained. More attention will be given to the respiratory gases in the blood plasma in the later chapter dealing with the vascular system.

The Voice.—Breathing is greatly modified when the expiratory air currents are used to vibrate the vocal cords in the larynx and thus produce sounds, as in talking or singing. In such cases, breathing is voluntarily controlled so that expiration is prolonged. The outgoing stream of air is then modified as necessary for the vibration of the vocal cords. And so the human voice, as well as the vocal sounds of other vertebrates, is the sound produced by vibrations of the stretched membranes. The pitch of the voice depends upon the amount of stretching. If the vocal cords are drawn tight, they will vibrate rapidly and produce a tone of high pitch, whereas the reverse condition will produce lower tones. The range of the pitch, which is important for singing, is dependent upon the amount of tension that can be placed upon the vocal cords by manipulation of the laryngeal cartilages, but the quality of the tone produced in speaking or singing is determined by a number of factors including the essential character of the cords themselves and the resonance of the throat region. Given wide range of tone and normal resonance, the singer will still be decidedly lacking in artistic accomplishment if unable to secure any desired pitch accurately and instantly. This is dependent upon the ability to adjust the cartilages of the larynx through muscular contraction so that just the right amount of tension will be placed upon the vocal cords. (Fig. 42.)

Speech represents definite modulations of the voice sounds issuing from the larynx, in order to produce the established letter sounds of a particular language. The modulation of the laryngeal voice is due to the actions of muscles in the throat, tongue, and lips. When once learned, the actions become essentially automatic, or reflex. The rather common impression that the tongue alone is responsible for speech is known to be erroneous, because, in cases where the tongue has been accidentally removed, the individual is able to produce most of the letter sounds in fairly intelligible fashion, but certain sounds in which the tip of the tongue is needed, as in the *th* sound, are defective. It is interesting to analyse the position of the tongue and lips and also

the control of the air stream in pronouncing the various letters of our language. Thus the vowel sounds *A*, *E*, *I*, *O*, *U* may all be produced by a continuous expiration through the open mouth, but each vowel requires certain adjustments of the lips to make the different letter sounds. The same air movement is found in *S*, *Z*, *F*, *J*, *V*, etc., but individual modifications in the mouth cavity are produced which involve both the tongue and the lips. *M* and *N* can be produced only by completely blocking the air passage through the mouth cavity and thus forcing the air through the nasal passages. Temporarily blocking both the mouth and the nasal passages by the lips or tongue results in explosive sounds necessary for such letter sounds as *B*, *P*, *T*, *D*, *K*, and *G*.

FUNCTIONAL FEATURES ASSOCIATED WITH RESPIRATION

The process of respiration, in which oxygen is received into the cells and carbon dioxide released from them, is, as we already know, a basic phenomenon of life which is universally present in every type of living cell. It is a continuous feature of the energy traffic between the organism and the environment made necessary by the fact that energy is required to maintain the life functions. These may be summarized as (1) metabolic, including the chemical activities necessary for enzyme digestion, for the synthesis of the protoplasmic material, and for the liberation of energy with heat production; (2) muscular activity; (3) nerve activity; and (4) secretory activity. About 80 per cent of the energy released in the body is utilized in the maintenance of body temperature. Life cannot exist without sufficient energy to maintain these vital activities, and energy cannot be secured except by oxidizing the organic materials in each individual cell. A muscle cell maintains its respiratory rate at a level sufficiently high to supply its own intracellular needs and to contribute its share to the work performed when the muscle of which it is a part contracts in response to a nerve stimulus. Likewise a nerve cell maintains its respiratory rate for individual needs and to contribute toward the maintenance of nerve function in the organism. So it is with every type of cell in the body. Finally the combined needs of all the cells are summated in the respiratory requirements of the individual.

Basal Metabolic Rate

It is possible for the physiologist to determine the amount of oxygen intake and carbon dioxide output necessary to maintain the metabolic activities of the body under varying conditions. The minimum rate at which the life processes can operate is known as the *basal metabolic*

rate (B.M.R.), and its determination is of considerable interest to the student of life activities but of particular importance to the clinician in the diagnosis of certain diseases, notably those associated with the thyroid gland. In order for the life functions to be measured at the minimum, or basal, rate, the individual must lie quietly, and voluntary muscle movements must be restricted so far as possible. Also no food is eaten for 12 hours previously so that the body is expending no energy in the digestive, assimilative, and synthetic processes. Thus the energy-liberating processes of the cells are at a minimum and sufficient only to maintain essential involuntary muscular movements associated

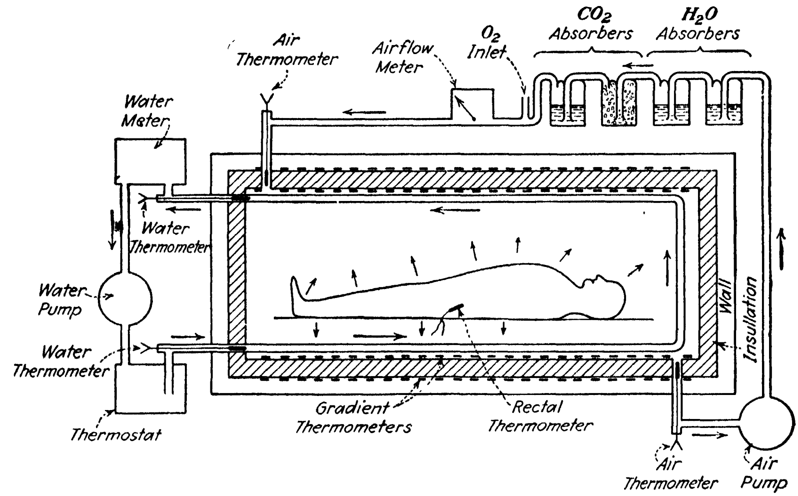


FIG. 47.—Diagram of calorimeter for measuring the basal metabolic rate of man. (*Watkeys, Daggs; after Murlin and Burton.*)

with breathing, circulation of the blood, etc., and to produce heat enough to maintain the normal body temperature. The latter requires by far the greater energy supplies and is taken as the measurement of the basal metabolic rate. This rate varies with age and in accordance with the surface area, and has been found to be in the neighborhood of 40 calories[1]—of heat per hour for each square meter of surface in a normal young adult.

There are two ways of determining the basal metabolic rate. In the first method, a person is placed in a calorimeter. This is an insu-

[1] The term *calorie*, as commonly used in physiology, is defined as the amount of heat that will raise the temperature of 1 kg. of water 1°C. (15 to 16°). This is known as the *large calorie* and is often capitalized as Cal. The *small calorie* (cal.) is one-thousandth of the large calorie, that is, the amount of heat necessary to raise the temperature of 1 g. of water from 15 to 16°C. Consult the Appendix: Calorie; Measurements.

lated chamber designedly large enough to admit the entire body of the experimental animal, which may include almost any size from a mouse to an elephant. The walls of the calorimeter contain water coils, and it is so equipped that normal breathing may occur. Heat is dissipated from the body of the individual through the lungs and skin and is measured by the increase in the temperature of the water in the walls of the calorimeter together with that of the expired air. A second method for determining the basal metabolic rate is by measuring the oxygen

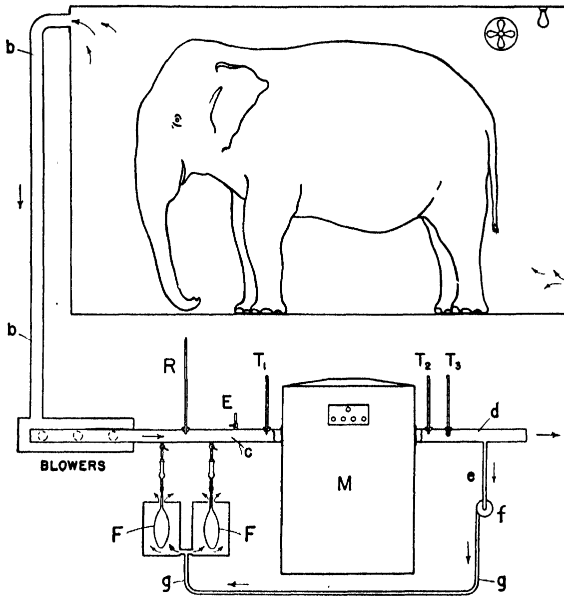


FIG. 48.—Diagram of calorimeter designed by Benedict for measuring the basal metabolism of an elephant. *a*, pipe for admission of outdoor air; *b*, pipe for air passing from calorimeter to be analyzed; *c*, pipe connecting blowers with meter (*M*); *R*, instrument for indicating rate of ventilation; *F*,*F*, rubber bags for collection of samples of air coming from calorimeter; T_1T_2, dry bulb thermometers; T_3, wet bulb thermometer; *d*, discharge pipe for air passing from calorimeter through meter to the exterior; *e*, pipe connecting with small blower (*f*) for forcing portion of air discharged from meter through pipe (*g*) into boxes enclosing sampling bags (*F*). (*Benedict, "Science in Progress," Yale University Press.*)

intake, inasmuch as the latter is always in direct ratio to the amount of materials oxidized and, therefore, the amount of energy released. Another factor that must be taken into consideration with this method is, however, whether carbohydrates, fats, or proteins are being oxidized, for each requires a different amount of oxygen, and each yields correspondingly varying amounts of heat energy. Thus 1 g. of glucose, when completely oxidized, produces 4.1 calories of heat. The oxidation of the same amount of a fat will produce 9.3 calories, but in so

doing only about 50 per cent more oxygen will be used than with glucose. In a word, it is clear that, when fat is being oxidized in the body, a given rate of oxygen intake shows a higher rate of heat production than when a carbohydrate is oxidized. (Figs. 47 to 49.)

Respiratory Quotient.—It is possible to determine whether carbohydrate, fat, or protein is being oxidized by the relationship between the volume of oxygen intake and volume of carbon dioxide eliminated. The relationship shown by dividing the latter (carbon dioxide eliminated) by the former (oxygen taken in) is known as the *respiratory quotient* (R.Q.). When a carbohydrate is burned, the volume of oxygen required is equal to the volume of carbon dioxide formed.

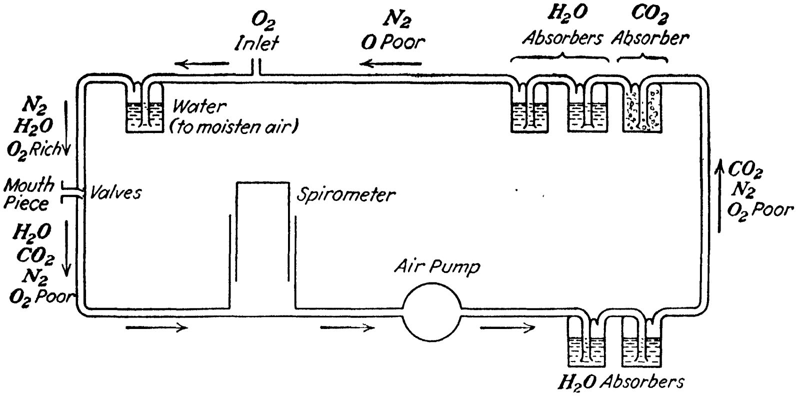


FIG. 49.—Diagram illustrating apparatus for determining the basal metabolic rate by measuring the oxygen intake. The patient breathes through the mouthpiece (left). The oxygen intake is measured when admitted to the system (inlet). The carbon dioxide output is measured by weighing the CO_2 and H_2O absorbers. (*Watkeys, Daggs.*)

This is seen from the equation $C_6H_{12}O_6 + 6O_2 = 6CO_2 + 6H_2O$, showing that the oxidation of sugar requires six molecules of oxygen, and releases six molecules of carbon dioxide; accordingly the respiratory quotient is 1.0. When a fat is burned, the amount of carbon dioxide released is less than the oxygen taken in. Thus each molecule of tristearin, with the formula $C_{57}H_{110}O_6$, requires 81.5 molecules of oxygen for complete oxidation, and only 57 molecules of carbon dioxide are released, which, divided by the oxygen consumption, gives a respiratory quotient of 0.70. The respiratory quotient, when protein is oxidized, is around 0.80.

Thus the respiratory quotient of a person with a high proportion of carbohydrate in reserve for oxidation will approach 1.0, whereas the inclusion of fat will reduce the respiratory quotient to lower levels. Inasmuch as the digestion, assimilation, and oxidation of carbohydrates are normally completed within a few hours after being received in the

alimentary canal, it is clear that the respiratory quotient of a person who has been deprived of food for some time will fall below the carbohydrate levels as the stored fats are increasingly oxidized in order to maintain the metabolic activities. It is found that the absence of food for 12 hours gives a respiratory quotient of about 0.74. In cases of severe fasting, which results in the depletion of the fat reserves as well as the carbohydrate, the respiratory quotient tends to approach 0.80 as the proteins of the cells are increasingly sacrificed on the altar of oxidation.

Normal Metabolic Rate

It is apparent that life could not be maintained very long at the basal rate, for a continual decrease in weight occurs as the energy requirements are supplied at the expense of the stored materials, and so, when a certain stage of starvation is reached, the activities necessarily cease. A more important question to the average person is the determination of the rate of metabolism reached in an active individual pursuing his daily routine and maintaining normal weight. This rate will be found to vary widely in different individuals depending upon their age, temperature conditions, and amount of muscular activity associated with their duties. The highest metabolic rate per pound of body weight occurs in the early years, when the child is not only very active all day long, but also new tissues are being formed continually. The lowest metabolic rate will be found in an inactive aged individual with a routine in which lengthy periods are devoted to resting in bed and sleeping. The one-year-old child requires the release of about 45 calories each day per pound of body weight, but the octogenarian, with his eighty or more years, requires about one-fourth of this caloric output, unless indulging in unusual muscular activity. The average man, weighing about 150 lb., requires about 17 or 18 calories per pound of body weight, or from 2,500 to 3,000 per day, when engaged in ordinary activities, which is about 10 per cent more than is required by a woman under comparable conditions. Under conditions of hard physical labor the rate is more than doubled, so that 7,000 to 8,000 calories may be required daily.

If the adult body weight is to be maintained, the foodstuffs eaten should supply enough calories to approximate the daily expenditure without oxidation of reserve materials. With too little food intake, the body weight will gradually be reduced; with too much food, there will be a tendency in the average individual to store up the excess materials in the form of fat. Fat accumulation, though, varies greatly in different individuals, and, occasionally, heavy eaters remain at

about the same weight over a period of years. In general, the appetite is the judge of the amount of food to be eaten; but unfortunately it is a fickle guide in many instances and tricks the individual into eating more than is necessary to supply the maximum metabolic requirements. Since the chemist can determine the exact number of calories that the various foods yield when they are consumed in the body, and the physiologist can determine the amount of calories required by the individual, it is possible to fix an adequate diet for each individual with great accuracy. If the diet is well balanced, it will not only satisfy the energy requirements but will also supply enough proteins to replace the nitrogen and other essential elements present in the broken-down tissues as well as those expended in the formation of various secretions, epidermal cells, hair, nails, etc. And, finally, it is essential that the vitamin requirements be met (page 57).

Hemoglobin, the Respiratory Pigment

The cells of the body have a contract with the vascular system to transport the essential materials to them from the collecting organs. Of first importance in this connection for oxygen transport is the respiratory pigment, hemoglobin, found in the blood of vertebrates. Other respiratory pigments having the same function and essentially the same composition are present in various invertebrate animals. These various respiratory pigments are all adapted for the transportation of oxygen to the cells. The vertebrate hemoglobin is localized in highly differentiated cells, the red blood corpuscles, whereas the respiratory pigments of the invertebrates are in solution. (Fig. 67.)

Hemoglobin is an exceedingly complicated protein compound with a high molecular weight in which the protein, globin, is combined with a heme pigment. The latter, in turn, consists of the element iron united to the pigment portion, porphyrin, which is commonly found in various plant and animal pigments. In the oxidized form, as in the blood, the heme pigment is known as *hematin*. Hematin, although constituting less than 5 per cent of the hemoglobin molecule, is certainly the portion of the molecule that has an affinity for oxygen. The belief is that this affinity is largely due to the presence of iron. Witness the readiness with which iron rusts as a result of the union with oxygen in the air. At any rate, hemoglobin is a great oxygen carrier. Experiments show that blood plasma with no red corpuscles cannot absorb more than 0.38 per cent of oxygen but that whole blood, containing the red corpuscles with hemoglobin, will absorb about

sixty times as much oxygen, or more than 20 parts of oxygen in 100 parts of blood. The chemical basis of oxygen transportation appears to be the ability of the hemoglobin to form with oxygen a definite, but unstable, compound, oxyhemoglobin. This new compound is more brilliantly red than hemoglobin and is characteristic of arterial blood, which has just received its full complement of oxygen during the passage through the lungs.

Oxyhemoglobin.—When oxyhemoglobin reaches the tissue cells throughout the body, it is changed to hemoglobin, and the oxygen released for entrance into the cell cytoplasm. It is now recognized that an intracellular ~~respiratory~~ pigment, cytochrome, is present in the cells, which is oxidized by the incoming molecular oxygen and presumably acts in bringing about ~~the utilization~~ of the oxygen in the cytoplasm. Specific enzymes are also present. The corpuscles, with the hemoglobin molecule restored, return to the lungs for a new supply of oxygen. The unstable nature of oxyhemoglobin, which is essential for the release of oxygen to the cells, is due to the relatively weak affinity existing between oxygen and hemoglobin.

This condition has its inherent dangers when some gas with a greater affinity for hemoglobin, notably carbon monoxide (CO), reaches the lungs, because a relatively stable hemoglobin-carbon monoxide compound will be formed to the exclusion of the oxyhemoglobin. In fact, in a mixture of equal parts of oxygen and carbon monoxide, the hemoglobin will take 250 parts of the latter to one of the oxygen. Accordingly, when air containing carbon monoxide is breathed (as may happen in a closed garage when the car is running or at night in the home when the carbon monoxide is released into the air by a faulty furnace) the red blood corpuscles will very soon be carrying large loads of the stable hemoglobin-carbon-monoxide compound and very little of the essential oxyhemoglobin.

Of great interest is the fact that the chemical composition of hemoglobin is closely related to that of chlorophyll, which is responsible for the synthesis of the organic compounds in green plants. In the chlorophyll molecule, magnesium is present in place of the iron that is essential to the hemoglobin molecule. Functionally, it will be remembered that chlorophyll releases free oxygen to the atmosphere during photosynthesis, whereas hemoglobin collects oxygen and carries it to the tissues. Chlorophyll, though present only in green plants, is indispenable as the agent for food synthesis essential to all types of life. Hemoglobin is not of so great biological importance, for it has no relationship to the plant world or to the lower types of animal life.

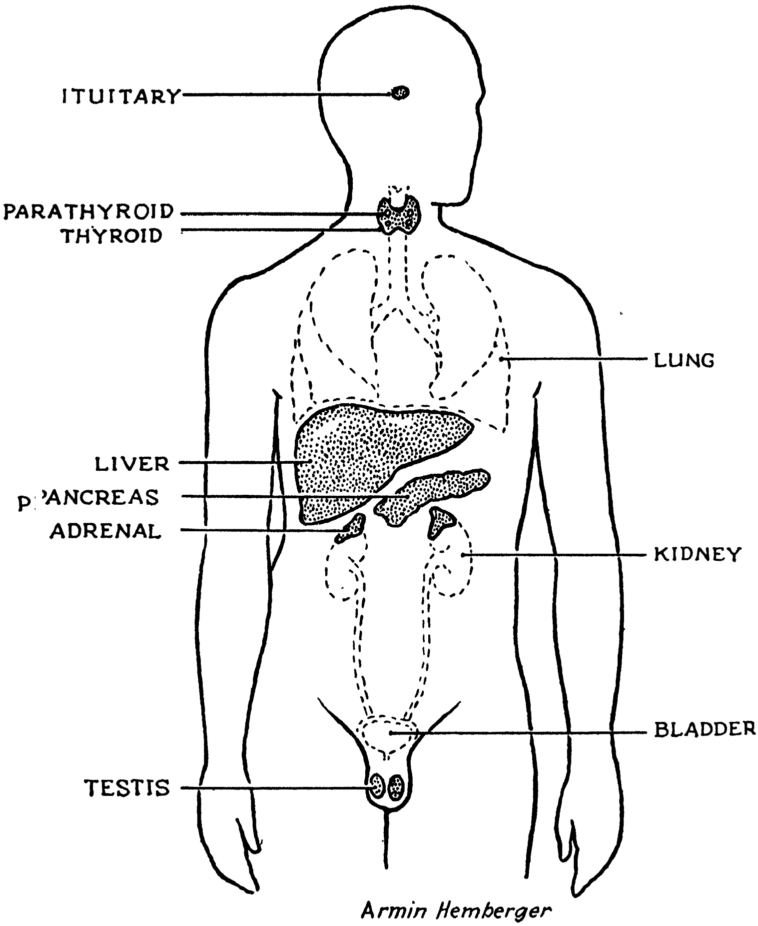


PLATE V.—Diagram to show the positions of the important endocrine glands (stippled) in the human male.

CHAPTER V

THE BIOLOGY OF SECRETION

Increasingly during the recent years, the underlying importance of the secretory processes in the living organism has been brought home to the biologist. At present, it appears that essentially all the life functions in the highly developed human organism are either based upon or closely associated with the process of secretion. Secretion seems to be a fitting and normal process for the digestion of food, but the uninitiated find it difficult to realize that various types of hormonal secretions are also responsible for the control of the general metabolic activities, including carbohydrate utilization in the muscles, growth, and reproduction. And recently it has become evident that the stimulus to muscle contraction is by a secretion rather than by a direct impulse from the nervous system. Possibly it is not over-emphasizing the situation to state that every cell in the organism secretes substances that make the internal environment more suitable for the other associated cells, that every cell gives to and every cell partakes of innumerable body secretions.

STRUCTURAL FEATURES ASSOCIATED WITH SECRETION

Secretions, as generally recognized, are synthesized in the cytoplasm of epithelial cells differentiated for that purpose. Such cells are known as *secretory* or *gland* cells, and, necessarily, they are very widely distributed throughout the body. In the previous chapters, they have been encountered in the skin, alimentary canal, pancreas, liver, trachea, etc. Secretory cells, either singly or associated in considerable numbers, constitute a gland. In the human organism, practically the only type of unicellular gland is the widely distributed goblet cell of the alimentary tract and associated structures which was previously described (page 52). Goblet cells manufacture the secretion mucigen, which is passed to the exterior through a tiny opening in the cell wall near the center of the free surface. Mucigen is chemically changed after secretion to form a protein substance, mucin. The latter in combination with water forms mucus, which is an important surface-protecting and lubricating material throughout the length of the alimentary canal, beginning with the nasal cavities.

The multicellular glands comprise a variety of types both structurally and functionally. The simplest type is found in a flat epithelial surface in which the undifferentiated epithelial cells in a restricted area are replaced by secretory epithelial cells, thus forming a multicellular gland. Such a condition is found, for example, in regions of the stomach mucosa. Increasing differentiation of the glandular area occurs in the larger multicellular glands, evidenced by the invagination of the secretory cells to form a depression, or pit, below the surface in the underlying connective tissues. In the simplest example of this,

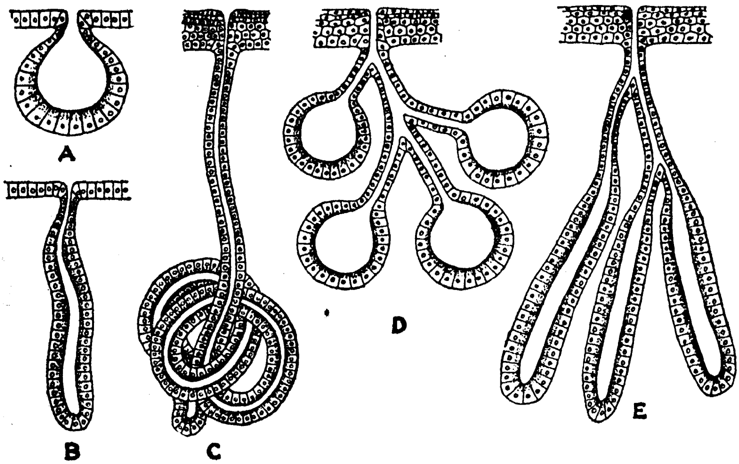


FIG. 50.—Various types of glands with ducts (exocrine). Diagrammatic. *A*, simple; *B*, simple tubular; *C*, coiled tubular gland; *D* and *E*, two types of compound glands. (*Wolcott.*)

the secretory epithelium forms a closed sac, microscopic in size, with a central cavity for the storage of the secreted materials and a duct leading to the surface. Such sac-like glands are walled off from the surrounding tissues by a basement membrane which is a type of connective tissue. They may be said to consist of the nonsecretory portion, or duct, and the secretory portion with the functional glandular cells. Glandular tissue must have an abundant blood supply, for the blood is the source of all their raw materials, and so it is found that the connective tissues immediately surrounding a glandular area contain dense capillary networks. In a sweat gland the secretory portion consists of a tightly coiled, tubular body surrounded by a capillary network. (Fig. 50*A*, *B*, *C*.)

From the simple sac-like gland with one secreting cavity, as just described, the larger and more differentiated types of glands are derived by subdivisions of the original cavity to form one or more

additional connected cavities, each lined by outgrowths of the glandular epithelium from the original cavity. These connected cavities are all closed sacs except for the opening into the common duct, and thus they form a compound secretory unit. A still larger and more complicated compound gland is formed by the association of several secretory units, or lobules, so that the several ducts unite to form one large surface opening which carries the products of several secreting areas. Such a compound gland may be thought of as tree-like in structure with the groups of leaves representing the secreting areas and the twigs, branches, and main trunk as being comparable to the ducts. A still further elaboration of glandular structure is to be noted in the mammary glands of the mammal female in which the surface opening, the nipple, has from 15 to 25 openings, each carrying the secretion, milk, from an individual lobe. Each lobe represents a grouping of the lobules of the compound glands. (Figs. 50*D*, *E*; 51.)

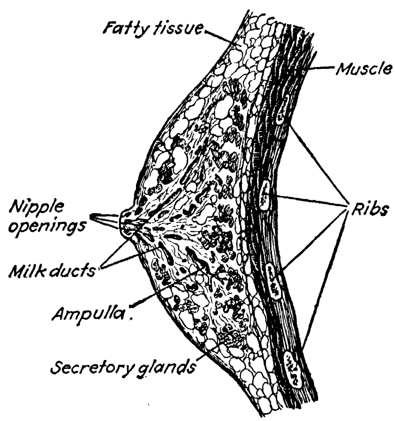
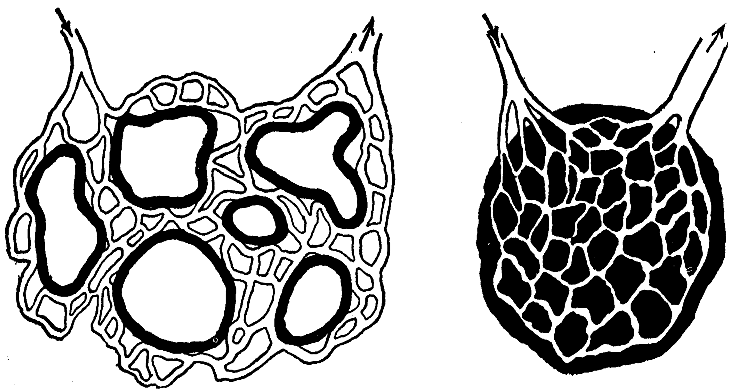


FIG. 51.—Vertical section through the mammary gland. Diagrammatic. (*Sherbon.*)

The glands of the body may be separated into (1) the exocrine type, as just described, in which each gland gives off its secretions through a duct opening at the epithelial surface, and (2) the endocrine type in which each gland has lost its connection with the epithelial surface and the duct is lacking. The endocrine glands, therefore, give off their secretions directly into the blood stream from which they are also constantly receiving their raw materials. Structurally, the endocrine glands are resolvable into two basic types: one in which the body of the gland consists of a group of separate sac-like secreting areas, separated from each other and entirely enclosed by connective tissue elements with abundant vascular tissues. In the other type of endocrine gland, the functional epithelium forms a single compact secretory unit which is permeated throughout by the capillary network. (Fig. 52.)

A number of important glands are both exocrine and endocrine and accordingly are known as *mixed glands*. Examples are found in the pancreas, liver, and testis. In the pancreas and testis, distinct types of cells are associated with the two types of glandular activities. In the liver, however, the histologists have been able to demonstrate

only one basic type of secreting cell. In general, the exocrine glands are associated with particular organ systems and are best considered in connection with such systems as has been done previously in the discussion of nutrition. The endocrine glands and the mixed glands are much more individualistic, so to speak, and will be discussed as independent units.



a b

FIG. 52.—Illustrating structure of endocrine glands. *a*, type, such as the thyroid and ovary, in which the secreting areas shown in heavy black lines are surrounded by connective tissue and blood vessels; *b*, type represented by the adrenals, pituitary, etc., in which the glandular epithelium is permeated by blood vessels, shown in white. (*Maximow-Bloom, "Histology," W. B. Saunders Company.*)

FUNCTIONAL FEATURES ASSOCIATED WITH SECRETION

The process of secretion should be clearly distinguished from that of excretion which is concerned with the formation and elimination of the cellular waste products. The chief excretions of the body are carbon dioxide, urea, and water, which result from katabolic activities in all the cells. Secretion is concerned with the intracellular synthesis of special substances which serve distinct functions in the organism and comprise a great variety of substances. In certain instances, however, the distinction between a secretion and an excretion is not clear. Thus sweat contains excretory material and is therefore designated as an excretion, but it may also be regarded as a secretion of the glands of the skin because it serves a definite function in connection with the control of the body temperature, Or again, carbon dioxide given off by every cell in the body is unquestionably an excretion, and yet it serves a very important and definite function in increasing the acidity of the blood and thereby influencing the respiratory center as was shown in the previous chapter (page 80). It is possible that many of the secretions may contain or be built around

excretory products of the cells, with the result that certain waste products of one type of cell can be utilized as a secretion by some other type. "One man's meat may be another man's poison."

The basic secrets associated with the manufacture of cell secretions lie deeply hidden in the metabolic activities of the particular cells concerned. About all that can be said is that the secretory cells have the power to take in the essential materials from the blood stream and synthesize a particular essential secretion. The latter may be of comparatively simple composition, as in urea, or so complex that the molecular structure still remains unknown. Every function of the body appears to be dependent upon one or more special secretions. But superimposed upon the secretions from the exocrine glands, which are concerned with some particular function of the body, are the secretions of the endocrine glands, known as *internal secretions*, or *hormones*, which aid in the regulation, control, and coordination of all the bodily functions and thus, in association with the nervous system, unify the life activities of the complete organism. This is a large order, and all the details are not yet known, but the broad outlines of the picture will be revealed in the following descriptions of the various endocrine glands and their hormones.

The term *hormone*[1] was first used about thirty years ago in connection with the discovery of secretin in the digestive tract. It is derived from a Greek word meaning *to excite*, and this is essentially what many hormones do, as has already been noted in the action of secretin in stimulating the pancreas (page 64), but some of the more recently discovered hormones are known to inhibit a certain function instead of increasing it. A hormone, then, may be said to be a specific substance given off by an endocrine gland and carried by the blood to some other organ where it produces a specialized type of reaction. Such a definition excludes certain endocrine secretions, notably the secretion of glucose into the blood by the liver, because glucose is universally used by all the cells. In general, the responses to the hormones, that is, chemical regulation, are slow, cumulative ones, which stretch over considerable periods of time, whereas the response to nerve control is very rapid. Exceptions are to be found, however, as in the adrenal secretion.

THE LIVER

Unlike the endocrine glands, the general importance and special activities of the liver as an exocrine-endocrine gland have long been known. The liver is the largest gland in the body and also one of the

[1] Consult Appendix: Hormones.

most versatile, with various essential functions closely linked to it and depending upon its normal activities. Its removal from an experimental animal invariably causes death in a very short time. Along with the pancreas, thyroid, and parathyroid glands, the liver develops as an outgrowth from the endodermal tissue of the primitive gut so that its functional tissues are of endodermal origin. Starting as a simple outgrowth, the liver gradually develops into a large compound gland with a weight in the human adult of from 50 to possibly 65 oz. A deep cleft partially divides the liver into right and left lobes, the right lobe being considerably larger.

The glandular hepatic tissue throughout the liver is separated into lobules of varying, but typically polygonal, shapes which are about the same diameter as a pin and roughly three times this in length. It is impossible to dissect out the individual liver lobules, however, because they are intimately bound together by the surrounding connective tissues and the vascular and conducting units. When a transverse section of a liver lobule is examined microscopically, the secreting or hepatic cells will be seen to be arranged in strands or cords which run radially from the center of a lobule to the periphery, like the spokes in a wheel. Between these hepatic spokes are irregular blood spaces, the sinusoids, which connect at the periphery with the incoming blood and at the center with the outgoing blood of the central vein. The latter continues centrally through the length of each lobule and in a transverse section is seen as the hub of the wheel. (Figs. 53, 54.)

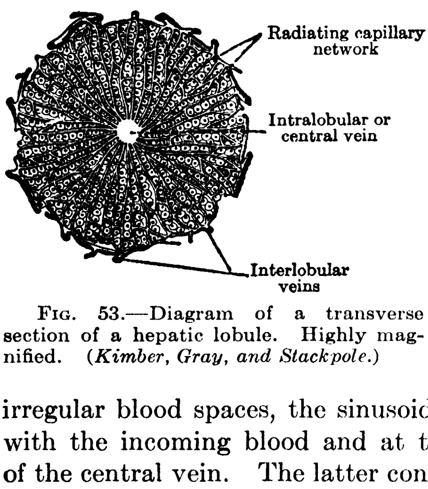


FIG. 53.—Diagram of a transverse section of a hepatic lobule. Highly magnified. (*Kimber, Gray, and Stackpole.*)

The liver is unique in that it has a double blood supply: one source through the hepatic artery and the other through the portal vein. The hepatic artery brings in a relatively small supply of arterial blood to the liver which, for the most part, supplies the connective tissues, whereas the large portal vein continually brings a large amount of blood from the alimentary tract, carrying the absorbed foodstuffs to the hepatic cells. It is the blood from the portal vein that flows through the open sinusoids of the lobules, in direct contact with the hepatic cells, thus permitting the latter to remove nutritive materials for chemical conversion and storage or to add secreted materials directly to the blood.

But the liver is not merely an endocrine gland secreting materials directly into the blood stream, for it also has a complete system of ducts ramifying through every lobule and carrying an exocrine secretion, bile, to a storage chamber, the gall bladder, from which it is ejected as needed into the duodenum. The ultimate units in the bile-collecting apparatus are the bile canaliculi, which form a tubular network throughout the lobules and actually tap every hepatic cell for its contribution of bile sap which ultimately reaches the gall bladder. The minute canaliculi unite to form larger ducts which lie between the lobules, and all these are finally consolidated to form the right and left hepatic ducts which come from the corresponding lobes of which the liver is composed. The right and left hepatic ducts unite as the common hepatic duct. The latter joins the cystic duct running to the gall bladder and, finally, continues as the common bile duct to an opening through the wall of the duodenum. The arrangement of the ducts may be thought of as Y-shaped, with the hepatic and cystic ducts forming the two upper spreading branches of the Y, and the common bile duct seen as the supporting upright. Bile collected in the liver passes through the hepatic duct to the junction with the cystic duct and then through the latter to the gall bladder. When bile is secreted, it passes from the gall bladder into the cystic duct and then through the bile duct to the duodenum. (Fig. 30.)

The gall bladder is a pear-shaped sac, holding some 2 fl. oz. of bile. It is about 4 in. long by 1¾ in. in diameter and, with the attached cystic duct, is shaped somewhat like a partially inflated toy balloon. The wall consists of muscular and connective tissue layers with a mucosa lining which shows considerable folding. The mucosa cells are highly absorptive in function and remove as much as 50 per cent of the water from the liquid bile received from the liver, thus concentrating the essential bile salts for use in the intestine when necessary for fat digestion. The release of bile into the intestine from the gall bladder is intermittent and in response to the action of a duodenal hormone, cholecystokinin, which causes a contraction of the muscular tissue in the wall of the gall bladder (page 102).

Functional.—The liver is an important nutritive organ, for, as noted in the chapter on Nutrition, the bile is concerned with the digestion and absorption of fats through the action of the bile salts. Even more important in respect to the nutritive functions of the liver is the control of the carbohydrate metabolism which it exercises through the formation of glycogen from glucose and its temporary storage, the reconversion of glycogen into glucose, and the secretion of the latter into the blood as needed to maintain the fuel requirements of the cells. Also of great importance is the ability of the hepatic cells

to convert excess amino acids from the digested proteins into an oxidizable carbohydrate by the deaminization processes (page 57). Finally, excess supplies of vitamins are stored in the liver, so that they are constantly available for nutritive requirements of the cells.[1]

The liver is an important excretory organ, for it is able to transform the various end-products of protein metabolism, thrown into the blood stream by every type of cell in the body, into urea $CO(NH_2)_2$ which can be excreted by the kidneys. Again the liver, in association with the spleen and bone marrow, acts as an excretory organ in the daily destruction of millions of worn-out red blood cells. The complete story of their dismantling is not known, but it is certain that the hemoglobin in the discarded red cells is changed to the dark-colored bilirubin which gives bile its characteristic color and finally leaves the body through the intestine. The valuable iron compounds, associated with the heme pigment in hemoglobin, are retained in the body and used in the formation of new hemoglobin.

The liver is an important vascular organ for, as just noted, it rids the blood of the old corpuscles and conserves the essential materials of the hemoglobin. In addition, more interchanges of materials en route to and from the blood occur in the liver than in any other organ. In part, these interchanges are concerned with maintaining body fluids at proper levels. It is estimated that there is more blood in the liver than in any other organ with the possible exception of the muscles. Finally, the liver prepares the material, fibrinogen, which is essential to blood clotting (pages 163, 167).

Among the most important functions of the liver is the protection of the body against poisonous substances and invasions of living parasitic bacteria from the alimentary tract. The chemistry of digestion is highly involved; the compounds formed during the process, particularly the partially digested proteins, are dangerous if received by the blood stream. Also, at times, foods may be eaten that are not in the proper state of preservation, and some of the contaminated material may get through the intestinal mucosa and into the portal vein. The liver stands as a barrier against the distribution

[1] "There is no evidence of specialization in the mammalian liver—indeed the evidence is definitely against it. Any or every cell seems capable of synthesizing glycogen from sugar or from lactic acid, of solving the chemical conundrum:—how to pass directly from carbohydrates to fats and back or proteins to fats, of dealing with metallic poisons, of controlling the chemical cycle of haemoglobin, of synthesizing uric acid, so on and so on. Has the biologist any picture even of the vaguest kind, of how so diverse a chemical factory can operate in a fluid mass, say 10^{-8} cubic millimetres in volume?" "To Remind—A Biological Essay," by Sir William Hardy, Williams & Wilkins Company.

to the body tissues of any and all unsuitable compounds that may be in the blood stream and, usually, is able to remove and destroy such substances before damage is done. In performing this function, the liver is really doing little more than it does in treating the nitrogenous wastes of the body cells and converting them to urea. But the liver

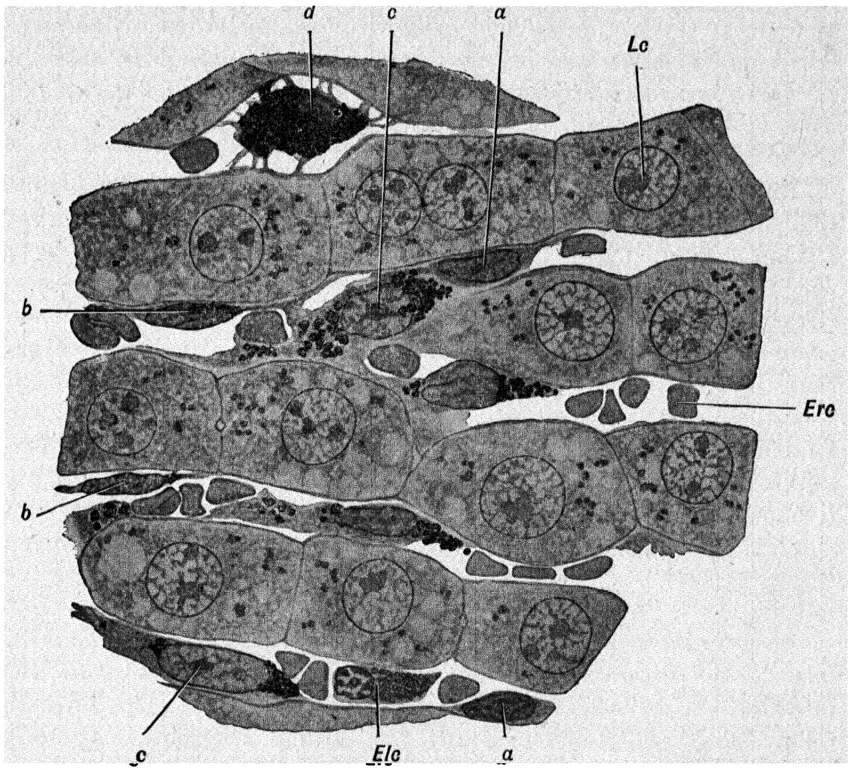


FIG. 54.—Drawing of a section of rabbit liver which has been injected intravenously with India ink. The figure illustrates a cell of Kupffer (*d*), gorged with ink particles, lying in the lumen of a sinusoid between the liver cells (*Lc*). Transition of the Kupffer cells from the resting state (*a*) to the active state (*d*) are shown in *b* and *c*. *Elc*, leucocyte; *Erc*, erythrocyte or red cell. Highly magnified. (*Maximow-Bloom*, "*Histology*," *W. B. Saunders Company*.)

also may be called upon to destroy living organisms, for the digestive cavities contain many bacteria, and, in rare instances, some of these parasites may get through the mucosa and into the blood stream. When the invaders reach the liver, they are eaten and destroyed by a particular type of amoeboid cell, the Kupffer cell, which is anchored in the liver sinusoids and give close inspection to all the materials present in the slow-moving blood stream. (Fig. 54.)

Endocrine Glands

It is possible to classify the endocrine glands in various ways, but perhaps the best arrangement for our purpose is to group them in accordance with the functions of the hormones that are produced. On this basis, three main divisions of the endocrines may be recognized as follows: (1) hormones concerned with the regulation of digestive functions, (2) hormones concerned with the regulation of metabolism, (3) hormones concerned with the general control of body functions.

Hormones Concerned with the Regulation of Digestion

Intestinal Mucosa.—The fact has been recognized for some time that some hormones are associated with the normal digestive processes in man. These are gastrin, secretin, and cholecystokinin, all three of which are secreted by the mucosal cells of the alimentary tract. Gastrin is secreted by the mucosa in the pyloric region of the stomach, whereas the other two are formed by the duodenal mucosa. More than thirty years ago it was found that, when mucosal tissue, secured from the lining of the stomach or duodenum, was ground up, an active fluid substance could be obtained from the material which, when injected into the blood stream, would incite secretory activity of digestive enzymes. Some authorities believe that the stimulating substances that cause the flow of gastric juices are liberated by certain of the ingested foods rather than by a hormonal secretion of the mucosal cells. Such foods are termed *secretagogues*.[1]

Secretin is formed by the duodenal mucosa cells and, when liberated into the blood stream, causes an active flow of pancreatic juice into the intestine. The flow of pancreatic juice is always exactly timed to follow the arrival of chyme from the stomach. The acid condition of the latter when it reaches the duodenal mucosa acts as an inciter for the hormonal activity of the mucosal cells. Accordingly the complete cycle of events includes the stimulation of the mucosa cells by the acid chyme, the liberation of the hormone, secretin, into the blood stream, the stimulation of the pancreatic cells by the secretin received from the blood, and, finally, the flow of pancreatic juice into the intestine. Coincident with the flow of gastric juice is the flow of bile from the liver. Until recently, it was supposed that secretin was also responsible for inciting the bile flow. It is now believed, however, that the latter is due to another mucosal hormone, cholecystokinin, also released by the duodenal mucosa following stimulation by the acid chyme. Cholecystokinin received from the blood causes a con-

[1] Consult Appendix: Secretagogues.

traction of the muscle tissue in the wall of the gall bladder. When the entire story is known, it will probably be found that still other hormonal actions are involved in the regulation of the digestive processes.[1]

Hormones Concerned with the Regulation of Metabolism

The Pancreas.—The important position that the pancreas occupies in the function of digestion has been indicated in the chapter on Nutrition; and in the paragraph just preceding, it has been shown

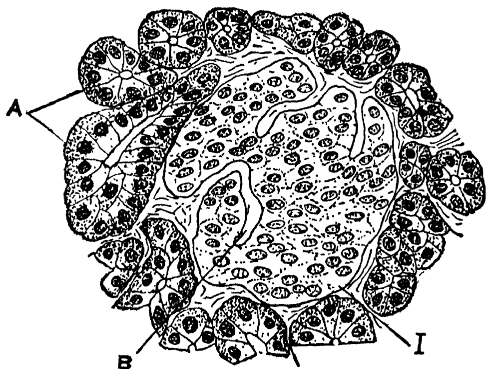


Fig. 55.—Section of pancreas, highly magnified, showing an Island of Langerhans (*I*) which releases its secretion directly into the blood vessel (*B*). This endocrine region is surrounded by the exocrine glandular alveolae (*A*) which secrete into the pancreatic duct. (*Wieman, after Stöhr.*)

that the pancreas is influenced in the secretion of the pancreatic juice by a hormone from the intestinal tract. The present final consideration of this remarkable organ has to do with its function as an endocrine gland, for included in its tissues are the islands of Langerhans which are responsible for the synthesis and secretion into the bloodstream of the hormone insulin which is essential to the regulation of carbohydrate metabolism of the body. The islands of Langerhans develop as bud-like outgrowths from the ducts of the glands that secrete the pancreatic juice, but they soon lose all connection with the ducts and form independent units which secrete their hormone directly into the surrounding capillaries. Insulin has been referred to as the carbohydrate hormone. Essentially, it is regarded as the "spark plug" of carbohydrate metabolism which is necessary to bring about the chemical union or oxidation of glucose and oxygen and the release of the potential chemical energy. In addition, it appears that insulin

[1] Consult Appendix: Cholecystokinin.

is necessary for the accumulation of the carbohydrate glycogen in the liver. (Fig. 55.)

An insulin deficiency in the body is due to a functional failure of the cells in the islands of Langerhans and is first marked clinically by the appearance of sugar in the urine, the condition known as *glycosuria*, or *diabetes*. Diabetes results from a partial cessation of the oxidative processes throughout the body tissues, particularly in the muscles, so that the amount of sugar in the blood is greatly increased. Associated with this is the almost complete depletion of the glycogen in the liver. The continuous demand for fuel to maintain the life processes and the unavailability of glucose in the absence of insulin soon cause the destruction of other nutritive cell substances in the cells. In particular, the utilization of the fat reserves results in the formation of poisonous substances, and acidosis develops. The latter, if not checked, leads to coma and death. It appears that the supplies of oxygen to the tissues are not sufficient for the complete oxidation of fats when comparatively large amounts of the latter are oxidized, and the poisonous compounds, ketones, are the result of incomplete combustion.

It was long recognized that the onset of diabetes was due to a diseased condition of the islands of Langerhans before it was possible to isolate the insulin from pancreatic tissue of cattle and other domesticated animals and to use it in the treatment of the human disease. The stumbling block in the isolation of insulin was primarily due to the fact that it is rapidly destroyed by trypsin, also secreted by the pancreas. This was finally circumvented by a special technique devised after years of research, and since then it has been possible to secure large quantities of pure insulin from the pancreatic tissues of animals slaughtered for food. The purified and crystallized insulin, thus obtained, contains 25,000 units per gram for the treatment of diabetes. In moderately severe cases of insulin deficiency, from 20 to 40 units of insulin per day is required. Unfortunately insulin cannot be taken by way of the digestive tract, because of the destructive action of trypsin and other proteolytic enzymes, but a solution must be injected under the skin and gradually absorbed into the blood stream. The insulin treatment for diabetes was first used in January, 1922; but in the intervening years, its use has become world-wide—the only remedy for millions suffering from insulin deficiency.

The Thyroid.—The human thyroid[1] gland consists of a pair of ovoid bodies lying on each side of the anterior end of the trachea,

[1] Consult Appendix: Thyroid.

closely embracing the larynx. The paired glands are covered by a connective tissue capsule and connected by the isthmus—a strip of glandular tissue crossing the ventral surface of the trachea just below the larynx. In the adult, the size of the thyroid varies considerably, with an approximate normal weight of about 1 oz. It is first seen in the embryo as an unpaired tubular structure which pushes out from the endodermal wall in the hind part of the mouth region. Histologically, the mature thyroid tissue is found to consist of a great many individual secreting units, separated from each other and all held together by the surrounding connective tissues which contain a very abundant blood supply. Each secreting unit, or follicle, is a tiny closed sac lined by the functional epithelium consisting of secreting cells. (Fig. 56.)

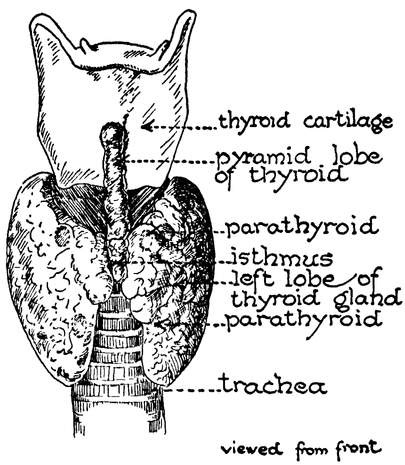


FIG. 56.—Drawing of the anterior end of the trachea, illustrating the position of the thyroid and parathyroid glands in man. Somewhat diagrammatic. (*Hunter, Walter, and Hunter, "Biology," American Book Company.*)

The thyroid follicles are normally filled with a secreted jelly-like material, the colloid substance, distinguished from all other compounds in the body by the fact that it contains a rich supply of iodine. Colloid substance contains the reserve supply of the thyroid hormone, thyroxine, the active principle of the gland. The complete hormone consists of a protein, globulin, in association with the active thyroxine. The latter was completely analyzed almost twenty-five years ago and found to have the formula $C_{15}H_{11}O_4NI_4$. The distinctive feature, as noted, is that it contains a large amount of iodine. Thyroxine is now synthesized in the laboratory, and the artificial product possesses all the characteristic properties of that naturally formed in the body, as tested by experimental animals.

Functionally, the thyroid hormone has a powerful effect in regulating the general metabolism of the body. A continuous supply of it is required at all times for normal functioning. The actual amount required, however, is amazingly small, due to its great potency; a characteristic that holds for all the hormones. It has been estimated that the amount of thyroxine circulating in the blood at any one time is about $\frac{1}{4}$ grain (about $\frac{1}{1750}$ oz.). Variations in either direction

from the normal amount will produce serious functional disturbances as will be indicated below. It is probable that thyroxine is largely concerned with carbohydrate utilization, as is insulin, but it apparently has a much broader base of action in the maintenance of essential environmental conditions for the body cells through the control of the composition of the tissue fluids, which must contain the proper substances and be free from excess waste products. These conditions are kept at the normal levels by nerve control, but the latter, in turn, is undoubtedly affected by the thyroid hormone. Endocrine disturbances develop in the body when there is too much or too little thyroxine. Thus well-marked clinical symptoms appear when a deficiency (hypothyroidism) occurs or when the level is above normal (hyperthyroidism).

Hypothyroidism indicates an insufficient supply of the thyroid hormone. The usual cause of this condition is a lack of iodine in the food supply, and this prevents the synthesis of thyroxine. Apparently in an effort to collect more iodine, the thyroid frequently enlarges to form a goiter which protrudes in the neck region. In time, a mass of tissue weighing several pounds may develop. Usually this so-called *colloid* type of goiter produces no ill effects except as a detriment to the personal appearance. Under other conditions, however, the overgrowth may invade the chest region and interfere with the respiratory activities. Hypothyroidism and goiter development are primarily due to a lack of iodine in the soil. Iodine is plentiful in the sea and in the soil of coastal regions, but various inland regions the world over show a more or less marked iodine deficiency with resulting pathological conditions appearing among the inhabitants and their domestic animals.

A deficiency in the thyroid hormone results in a marked lowering of the basal metabolic rate (page 85). This is due to an inability of the cells to maintain the normal oxidative rate. Even with reduced intake of food—generally the appetite of the sufferer is poor—a noticeable increase in fat storage occurs in the hypothyroid individual. The temperature of the body falls in correspondence with the reduced oxidation, and the patient feels chilly. If the thyroxine deficiency persists, the skin becomes thick, rough, and puffy with a peculiar consistency. But worst of all, hypothyroidism causes a steady deterioration of the nervous functions and may result in a complete breakdown of the higher mental processes. The brief outline just given summarizes the results of thyroid deficiency in the adult, a condition known as *myxedema,* which is somewhat different from the cretinism that develops in children from the same cause.

Children born in regions where the iodine deficiency is such that mothers have had an insufficient supply of thyroid hormone during pregnancy are often misshapen at birth, with bloated face, thick protruding tongue, pot-bellied abdomen, and abnormal mental development. They are known as *cretins*. The same cretinous condition may also develop in children after birth if the food supplied does not contain the necessary amount of iodine. Until comparatively recently, such unfortunates were doomed to as sad an existence as could be imagined, but the discovery that supplying thyroid gland substance of some animal in the food would almost miraculously relieve the condition—and this applies to adult myxedema as well—flooded the cretinous stage with a new life light. As Osler says:

> Not the magic wand of Prospero or the brave kiss of the daughter of Hippocrates ever effected such a change as that which we are now enabled to make in these unfortunate victims, doomed heretofore to live in hopeless imbecility, an unspeakable affliction to their parents. . . .

Hyperthyroidism is usually due to an abnormal activity of the thyroid gland and the consequent production and distribution throughout the body of an excess amount of the hormone. The same hyperthyroid condition, however, obtains when too much thyroid material is taken into the body through the digestive tract, as sometimes happens when an overenthusiastic "reducer" unwisely uses the hormone in an attempt to reduce the body weight. The latter cause of hyperthyroidism is easily remedied by changing the diet, but the first cause can be relieved only by the removal of a portion of the overactive gland. The underlying causes of thyroid superactivity are not apparent. Dietary factors apparently are not responsible as in hypothyroidism.

The reaction of the body mechanism to an excess of thyroid hormone is essentially the reverse of that when hypothyroidism occurs. Thus a decided increase in the basal metabolism occurs, which means more oxidation and increased body temperature. More nitrogen is eliminated through the urine which indicates that the protein metabolism is also affected to some extent. The circulation of blood is stepped up, and the nervous system is definitely more sensitive. The person tends to be active, irritable, at high tension. Possibly the general effect in the body may be compared to the action of the motor when the driver steps on the accelerator. These preliminary symptoms, characteristic of hyperthyroidism, herald the approach of the serious disease condition known as *exophthalmic goiter* which, in addition to an exaggeration of the symptoms just indicated, is further

marked by protruding eyes, dangerous overstimulation of the heart muscle, and, finally marked nervous disorders.

In summary, Hoskins has well said with reference to the general effects of the thyroid gland:

> This much we know. We are what we are in no small measure by virtue of our thyroid glands. Our development before birth and through infancy depends upon their functional integrity. The hurdles of puberty are taken with their aid. A pinch too little of thyroid spells idiocy. A pinch too much spells raving delirium. By its very mobility the thyroid plays a major role in keeping us attuned to our environment. Nature has done much with the thyroid hormone.[1]

The Parathyroid Glands.—The parathyroids in the human organism usually consist of four oval-shaped bodies, each about the size of a pea. Both in their development and later location in the body, they are in close association with the thyroid glands, as indicated by the name given to them. Functionally, however, it is rather surprising to find that the parathyroids have little or nothing in common with the thyroid apparatus, and in that way the name is misleading. The parathyroids are so small and lie in such close apposition to the thyroids, or even actually embedded in the thyroid tissue, that for long years they were regarded as misplaced bits of thyroid tissue. (Fig. 56.)

Surgeons were the first to recognize that functionally the parathyroids were entirely distinct from the thyroids, for they found that, in the surgical removal of portions of the thyroid to relieve disease conditions associated with hyperactivity of that gland, the parathyroids would, not infrequently, be injured or even removed. When this occurred, distressing symptoms unassociated with normal thyroid removal quickly made their appearance, and in cases where great damage had been done to the parathyroids, the patient always failed to survive. When the nature and importance of the parathyroids were finally recognized, great care was taken in thyroid operations to see that they were left undisturbed.

The parathyroid hormone coming from these tiny endocrine glands is almost infinitesimal in amount, and accordingly it has never been subjected to chemical analysis, though an active substance has been isolated which is believed to be the hormone. Inasmuch as the hormone is digested in the alimentary tract, it apparently has a protein nature as in the case of insulin. It has, however, been established by experiments on various animals that the parathyroid hormone is primarily concerned with the control of the calcium metabolism of the

[1] Hoskins, "The Tides of Life," W. W. Norton & Company, Inc.

body. This common element is an important constituent of our bones and teeth, but, in addition to this, the normal blood always contains a small amount of calcium, about 0.01 per cent. Small as is the amount of calcium in the blood, it is absolutely essential that it be present at all times, and the maintenance of the proper levels is the function assigned to the parathyroid hormone. This is apparently accomplished, for the most part, by aiding in the absorption of calcium from the alimentary tract when more is needed, also by aiding in the elimination of calcium from the body when the level is too high. Furthermore, it can be shown experimentally that an excess of parathyroid extract will cause a depletion of the bone calcium.

Authorities are in general agreement that calcium is necessary to keep the nerve and muscle tissues at the proper degree of irritability. Essentially the action of calcium appears to be that of a sedative, for when the calcium supply falls below normal, greatly increased irritability is at once noted. The muscles contract spasmodically and more and more violently, until the organism is in a state of tetany. This muscular activity apparently is due to the increased irritability of the motor nerves, for the latter are further stimulated by the contracting muscles so that a vicious circle is soon set up. Some authorities hold that the maintenance of the proper calcium-phosphorus ratio in the body is also tied up in the general parathyroid complex.

Tetany is a condition in which the muscles become rigid, as in convulsions, with stiffened limbs and clamped jaws. In the experimental animals, tetany rapidly follows removal of the parathyroids and ends fatally unless parathyroid extract is supplied. The latter seems almost miraculous in the relief it brings, but this, of course, is only temporary if the glands have been completely destroyed. The injection of calcium salts into the blood stream has essentially the same effect as the administration of parathyroid extract. There seems to be no question, therefore, of the basic relationship between the parathyroid gland and calcium metabolism, though probably the whole story is not yet known.

It was noted above in the discussion of the thyroid that both hypothyroidism and hyperthyroidism are not uncommon. This is not the case with the parathyroid, for it apparently gives very little trouble except when it is accidentally disturbed in surgical operations associated with thyroid removal.

The Adrenal Glands.—The paired adrenal[1] glands are always found in close relationship with the kidneys and were, therefore, long thought to be linked with the kidneys functionally as well as anatomically. This proved not to be the case, and no functional reason seems to exist

[1] Consult Appendix: Adrenal.

for their position in close contact to the anterior end of each kidney. Each adrenal gland weighs slightly more than ⅓ oz., is flattened and roughly triangular in shape. If the gland is sectioned and the cut surface examined, it will be found to consist of two distinct regions: an outer thicker shell, the cortex, light yellowish in color; and an inner, brownish-red portion, the medulla, making up the rest of the gland. The cortex and medulla have different origins in the embryo, the former coming from the mesoderm of the body cavity, whereas the latter is derived from the ectoderm in close association with the autonomic nervous system. (Plate *V*, page 92.)

The cells of the adrenal cortex are arranged in three poorly defined layers, or zones, and are characterized by the presence in the cytoplasm of various lipoids. The microscopic structure of the medulla is quite different from the cortex and resembles somewhat the condition in the liver lobule, described in this chapter, in that groups or cords of cells are separated by the tiny channels or sinusoids through which the blood flows (page 101). Thus the cells are in close contact with the blood—in fact, the cells may be said to form the banks of the stream—which makes it very easy for materials to be received or given off. The cells of the medulla are closely associated also with the cells of the autonomic nervous system, which are distributed generally through this region. The adrenal gland is marked by an extraordinarily rich blood supply. It has been estimated that six times its own weight of blood passes through the adrenal every minute, which probably makes it one of the most highly vascularized of all the tissues of the body.

Just as the two portions of the adrenal show marked structural differences, so do they also exhibit characteristic functional differences, for they produce separate hormones. The hormone from the cortex of the adrenal, known as *cortin*, has been isolated for only a few years, and its chemical composition, as well as its function or functions in the normal animal, remain largely undisclosed. That cortin is vitally important no one can question, for, when the cortex is removed from an experimental animal or when it is destroyed by disease in man (Addison's disease), the life functions of the organism cannot long be maintained. Possibly, of course, the adrenal cortex may be essential for the removal of some poisonous body waste, but there seems to be an entire lack of evidence of such a function. And on the other hand, the fact is established that the lives of experimental animals with the cortex removed and human beings with cortex destroyed by disease can be prolonged by the injection of cortin. Animals with the cortex removed show a marked drop in the basal metabolic rate and a disturbed carbohydrate metabolism. In association with these patho-

logical symptoms, the temperature control is disturbed and the kidneys fail to function adequately. All of these functional abnormalities develop from the lack of cortin, but they throw very little light on the functions of cortin under normal conditions. Like insulin, this hormone is rapidly destroyed by the digestive enzymes, and, in addition, cortin is difficult to isolate. The yield is small by any method yet devised. Another hormone, adrenosterone, with characteristics similar to the male hormone, has recently been obtained from the adrenal cortex.

The hormone from the medulla of the adrenal gland, variously known as *epinephrine*, *adrenaline*, and *adrenin*, has been isolated, chemically analyzed, and widely used in medicine for over thirty years. Compared to many other of the nitrogenous compounds associated with the living organism, it is relatively simple in its chemical structure, with the formula $C_9H_{13}O_3N$. The use of this substance in medicine, where it has been found to be of particular value in the alleviation of asthma and hay fever and in stopping hemorrhage by inducing contraction of blood vessels, is very different from its normal use in the body, which is best described by the term *emergency hormone*. Adrenin may be said to make better fighters of us all and to be essential when all the organs of the body must be operating at their highest rate.

It has been seen above that the tissues of the medulla develop and remain in partnership with elements of the autonomic nervous system. The autonomic system controls the vital organs of the body; and, when necessary, its call to action is reinforced by the adrenin poured into the blood, thus reaching all the organs of the body in less time than it takes to tell it. As a result, the heart beats faster, the liver releases additional carbohydrate for fuel, and increased oxygen intake occurs. At the same time, the blood vessels supplying the skin and digestive organs contract so that more blood laden with essential materials can be sent to the muscles. In short, under the stimulus of adrenin all possible is done by the body tissues in order to permit the maximum amount of carbohydrate metabolism in the muscles, with a corresponding release of energy made available for a foot race, a ball game, or the more serious duties with which everyone is confronted from time to time.

Hormones Concerned with the General Control of Body Functions

The Pituitary Gland.—The small unpaired gland, known as the *pituitary*[1] or *hypophysis*, is attached to the underside of the brain by a

[1] Consult Appendix: Pituitary.

short stalk. An inexperienced person dissecting the brain of even a good-sized animal would probably never notice the pituitary and so would remove the brain and leave the pituitary, with a tiny bit of its stalk lying snugly in a little bony cavity of the skull which is built around it. But, nevertheless, the pituitary was early discovered and long thought to be a gland for the secretion of the fluid mucus used to lubricate the throat surfaces. The human pituitary is about the size of a large pea and consists of an anterior lobe and a posterior lobe with an intermediate area lying between them. The origin of these two portions of the pituitary is diverse. Thus the anterior lobe develops very early in the embryo as a tiny outpocketing from the roof of the mouth cavity. This ectodermal sac then proceeds to grow anteriorly toward the brain until it meets a tiny body of nerve tissue, the infundibulum, projecting from the floor of the brain. The infundibulum becomes the posterior lobe of the mature pituitary. (Fig. 57.)

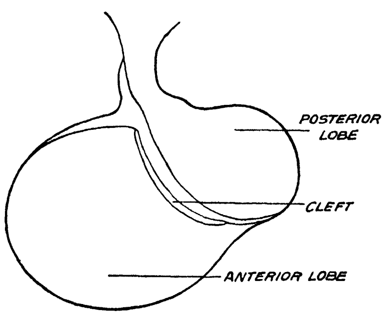


FIG. 57.—Section through the adult human pituitary. Diagrammatic. (*Redrawn from Hoskins, "The Tides of Life," W. W. Norton & Company, Inc.*)

The pituitary and the liver are certainly the two most versatile glands in the body (page 99). It might be difficult to determine which one should be awarded the prize for association with the most functional activities. But the liver, with its enormous size, looks the part, whereas the insignificant pituitary gives no structural indication of its importance. Furthermore, the relationship of the pituitary with other organs is not as a minor agent, for it is the actual controlling power—the generalissimo, if you will—directing the activities of various glands, of numerous major functions. This pituitary control is accomplished through various specific hormones—at least eight separate ones are believed to be produced by this bit of glandular tissue—most of which are formed in the anterior lobe. The microscopic examination of tissue from the anterior lobe shows much the same cellular arrangements as in the medulla of the adrenal; that of the posterior lobe appears to be almost barren of secreting cells. Altogether, there are not nearly enough differentiated cell types to account for the variety of hormones produced by the pituitary.

Possibly the best conception of the pituitary in the limited space available may be gained by presenting a short summary of the hormone actions as known at present. Such a summary will undoubtedly

need considerable revision as the years go by, for the pituitary research field is one of the most active known to biology, and major problems are still unsolved. However, this same statement holds true, in general, for the entire field of endocrinology.

Pituitary hormones are able to control the growth processes in the body as a whole, as well as that of certain organs. It has long been recognized that an excess, during the formative years, of anterior lobe hormone from an enlarged pituitary gland results in gigantism. Instances are recorded where such individuals have attained a height of around 9 ft. Apparently one of the best examples of gigantism ever recorded died recently in Illinois. The young man was only about twenty-one years of age at the time of his death, but had reached a height of nearly 8½ ft. and a weight of around 400 lbs.

Where the excess of the pituitary hormone is available during the developmental period, it results in a symmetrical overgrowth of the body tissues generally. A somewhat different result is evident when the enlargement of the gland occurs in later life, after adult size has been reached, for then a fatal disease, acromegaly, develops—a term that literally means "big extremities" and clearly describes the situation. Acromegaly is characterized by a gradual enlargement of the bones of the hands, feet, and face. It is only slightly noticeable in the early stages but gradually results in the production of a grotesque caricature of the earlier normal condition. Both the post-mortem examinations and the results from experimental animals confirm the belief that acromegaly is due to an excess of a pituitary hormone.

On the other hand, a deficiency of the pituitary and other hormones results in a type of dwarfism that may be regarded as the reverse of gigantism. Such an individual appears to be essentially a miniature of the normal adult with a symmetrical development throughout the body, generally pleasing appearance, and intellectually capable. Such midgets are to be distinguished from achondroplastic dwarfs in which a large head and features are placed upon a child-sized body. The developmental basis of the midget type is not known. Pituitary insufficiency is also believed to be responsible for the so-called "Frohlich's syndrome" in which a marked condition of obesity develops in childhood or early maturity. Dickens evidently described such a case in the Fat Boy of "Pickwick Papers." (Fig. 58.)

Pituitary hormones from the anterior lobe exercise definite control over the activities of certain other important endocrine glands. This fact has been established in the cases of the thyroid, adrenal, and sex glands. For instance, experiments on rats have shown that the removal of the anterior lobe of the pituitary results in marked degenera-

tive changes in the secreting cells of the thyroid together with the practical destruction of the adrenal cortex. Closely associated is the control over the sex glands, both testes and ovaries, exercised through one or two specific hormones (Prolan *A* and *B*). A wide array of experimental results show that the gonads and associated structures of various mammals are stimulated in a number of ways. Thus it has become laboratory routine to stimulate egg production in the amphibia

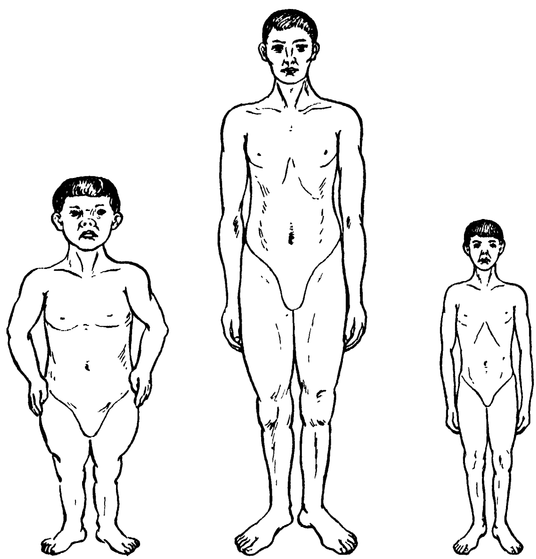


FIG. 58.—Illustrating the body form of a normal adult man (center) as compared with an achondroplastic dwarf (left) and the small, graceful form of a true midget (right). (*Redrawn from Stockard, "Physical Basis of Personality," W. W. Norton & Company, Inc.*)

out of season by pituitary extract.[1] In most cases, the pituitary hormones work indirectly by stimulating the production of sex hormones in the testis or ovary, and the sex hormones thus produced incite the changes in the sexual apparatus as a whole.

Closely associated with the reproductive function is milk formation, or lactation, in the mammalian female. An active pituitary principle,

[1] The following advertisement recently distributed by the General Biological Supply House is pertinent in this connection: "Once upon a time teachers could obtain living frog eggs for only a week or so in the early spring, but such specimens are now available throughout the entire school year. And you can, if you wish, perform the entire experiment in your own laboratory. Our Frog Pituitary Set includes two living male grassfrogs, one living female grassfrog, one unit of frog pituitary suspension and simple but detailed directions for producing laboratory-induced eggs."

prolactin, has been isolated which stimulates this activity. Finally, there seems to be quite general agreement that pituitary hormones exercise final control over the utilization of carbohydrates, fats, and proteins in the body. Thus, in carbohydrate utilization, abnormal activity of the pituitary will result in an increase of blood sugar and its elimination through the kidneys just as does the lack of insulin. Reciprocally, pituitary hormone deficiency results in a fall of blood sugar below normal levels. And in the case of protein utilization, an excess of pituitary extract apparently results in the storage of greatly increased amounts of proteins.

At least two separate hormones are believed to be produced by the posterior lobe of the pituitary. They have not been isolated, and the results are obtained by the use of glandular extracts. The hormones of the posterior lobe are primarily associated with the contraction of smooth muscle tissues, particularly in the walls of the blood vessels, and this results in an increase of the blood pressure. Another distinct pituitary function is associated with greatly increased urine secretion. This appears to be associated with a decrease in water absorption by the cells of the body. In other words, the direct effect of this hormone is on the body cells rather than the kidney.

The Gonads.—The detailed consideration of the gonads may well be deferred until the function of reproduction is described in a later chapter; but at this point, mention should be made of the hormonal activities of these organs which have very important functions in human structure and physiology. The male gonads, or testes, include, in addition to the tissues concerned with the production of the male sperm, an endocrine tissue situated in the areas between the sperm-producing tissues. This glandular, or interstitial tissue consists of secreting cells which are distinct from the germinal tissue. The castration of male domestic animals and even of man himself (eunuchs) has been practiced from early times and has always been followed by a modification of the secondary sex characteristics, that is, the distinctive structural features associated with the two sexes. In castrated males, if done when young, the results are: increased body size, a wide distribution of subcutaneous fat which alters the body shape, and a modification of normal behavior. These changes result from the lack of the male sex hormone, testosterone, secreted by the interstitial tissue. It has recently been possible to isolate this male hormone, and in 1934 it was artificially synthesized in the laboratory.[1] The injection of testosterone in a castrated animal will gradually induce the formation

[1] The isolation of the male hormone was accomplished by a Swiss investigator, Ruszicka, who received the Nobel Prize for this work in the fall of 1939.

of the normal male secondary sex characteristics.[1] It is well established that the final control of the sex hormone secretion is normally a function of the pituitary hormone. (Fig. 59.)

The female gonads, or ovaries, are known to secrete at least two sex hormones, but they are not produced by endocrine tissues lying between the reproductive tissues as just noted in the case of the testis.

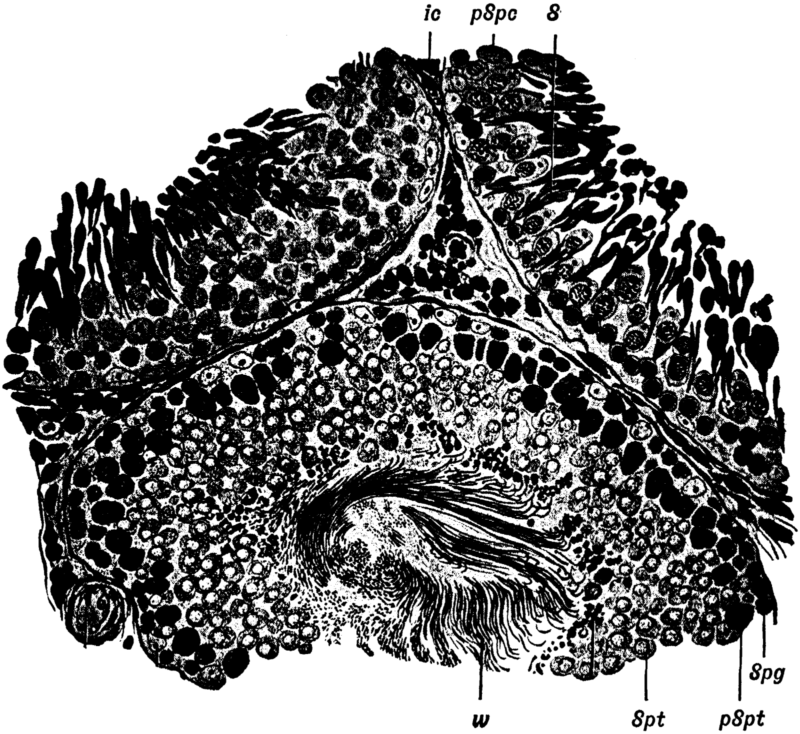


FIG. 59.—Section through the mammalian testis (rat). Highly magnified (× 250) to show the interstitial tissue (*ic*) which secretes the male hormone (testosterone). Note that the interstitial tissue lies between the seminiferous tubules. Various stages in spermatogenesis are shown as described in Chapter XIII. (*Maximow-Bloom, "Histology," W. B. Saunders Company.*)

As the ovarian eggs mature, each is enclosed by a liquid-filled vesicle, the Graafian follicle. One of the female sex hormones, estrone, is produced by the associated follicular cells. It is clear that this hormone is not responsible for the development of the secondary female characteristics but is concerned with the preparation of the uterus for the implantation of the fertilized egg. Apparently estrone is first secreted at the time of puberty, under the stimulation of the pituitary hormone. The other ovarian hormone, progesterone, is also formed

[1] Consult Appendix: Sexual Characteristics.

in the follicles but by an endocrine tissue, the corpus luteum, which is not formed until after the eggs have been released. Progesterone, secreted by the corpus luteum, acts on the muscular uterine walls and on the entire genital apparatus as well. It prevents the normal monthly cyclical changes if the egg is fertilized and a pregnancy develops. In case the egg is not fertilized, the corpus luteum soon begins to degenerate, loses its endocrine function, and the ovarian

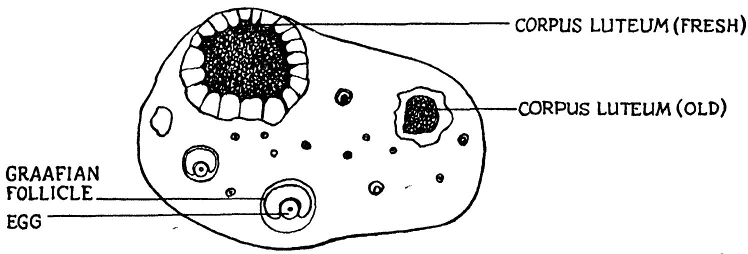


Fig. 60.—Section through human ovary to show the corpus luteum, an endocrine tissue. Graafian follicles, with eggs, in various stages of development are also indicated. Diagrammatic. (*Redrawn from Shull.*)

cycle is resumed (Fig. 60). Progesterone may thus be said to be particularly concerned with pregnancy. A hormone similar to progesterone in its function is also produced by the placenta during pregnancy. It has also been shown that the chemical composition of the male hormone, testosterone, and the female hormone, estrone, are very close and that these hormones will function, to a certain extent, interchangeably between the two sexes when injected in the opposite sex. Consideration of the reproductive processes in a later chapter will give further opportunity for a discussion of the reproductive cycle.

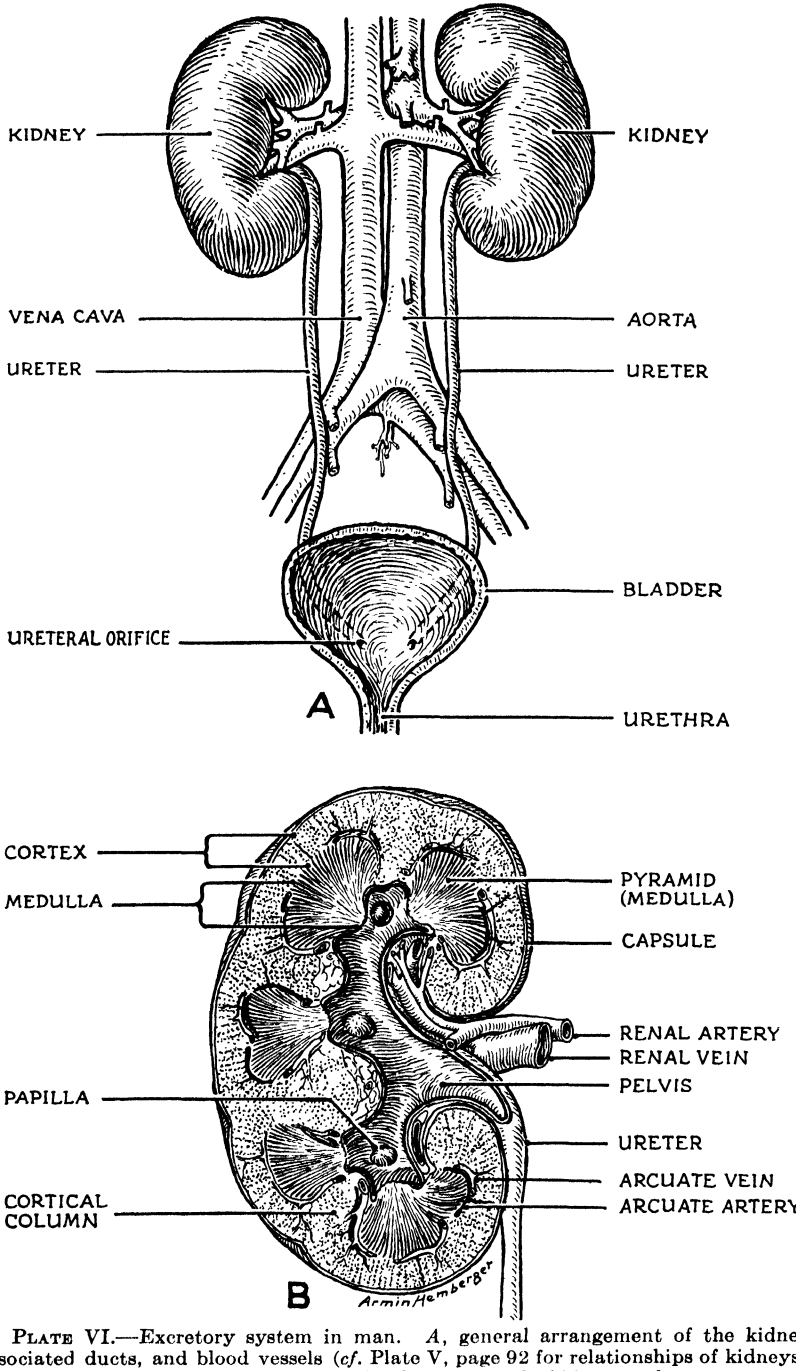


PLATE VI.—Excretory system in man. *A*, general arrangement of the kidneys, associated ducts, and blood vessels (*cf.* Plate V, page 92 for relationships of kidneys to other organs). *B*, drawing of a longitudinal section of the kidney to show arrangement of tissues.

CHAPTER VI

THE BIOLOGY OF EXCRETION

The chemical activities associated with the life metabolism of the cells in the body continually produce waste products that, for the most part, are not only useless but actually harmful to the continued existence of the cells themselves. Continuous removal of these wastes from the individual cells and their elimination from the body is, therefore, essential to the maintenance of the life processes. This activity constitutes the function of excretion. It is well to distinguish between excretion and egestion; the latter function being concerned with the elimination of materials that have not been associated with the protoplasm of the organism, in particular, the egestion of indigestible refuse from the alimentary canal.

Excretion requires part-time service from several organ systems in addition to full-time service from the kidneys, which are commonly regarded as the basic excretory organs of the body. Thus the important relations of the skin, of the lungs, and of the liver to excretion have been indicated in previous chapters. Later it will be apparent that the vascular system, as the transporting unit for the excretory products, is also an essential part of the complete picture. All of these organs working together are able to relieve the body cells of the useless end products of intracellular life chemistry, consisting of carbon dioxide, water, inorganic salts, bilirubin, and various nitrogenous compounds, notably urea.

EXCRETION AND THE SKIN

In its capacity as an excretory organ, the skin of man is concerned with the elimination of sweat which, secreted by sweat glands, leaves the body through the pores opening at the skin surface (page 37). A chemical analysis of sweat shows that it consists of from 98 to 99 per cent water, with slight amounts of carbon dioxide and nitrogenous wastes in solution. The total amount of perspiration given off each day is subject to wide variation, for, as previously indicated, it is dependent upon the amount of work performed, the amount of water absorbed from the alimentary tract, and the temperature of the external environment. Strictly speaking, only the first of these, that is, the amount of work performed, is primarily concerned with excretion, but

the other two, particularly the environmental temperature, are important in the complete picture of skin activity. Energy to do work comes, as we have seen, from the breakdown of glucose into carbon dioxide and water. Very small quantities of carbon dioxide and varying amounts of water are eliminated by way of the skin. The total of these two compounds to be eliminated varies directly with the amount of sugar oxidized. Of these three factors, the external temperature is probably the most decisive in determining the sweat

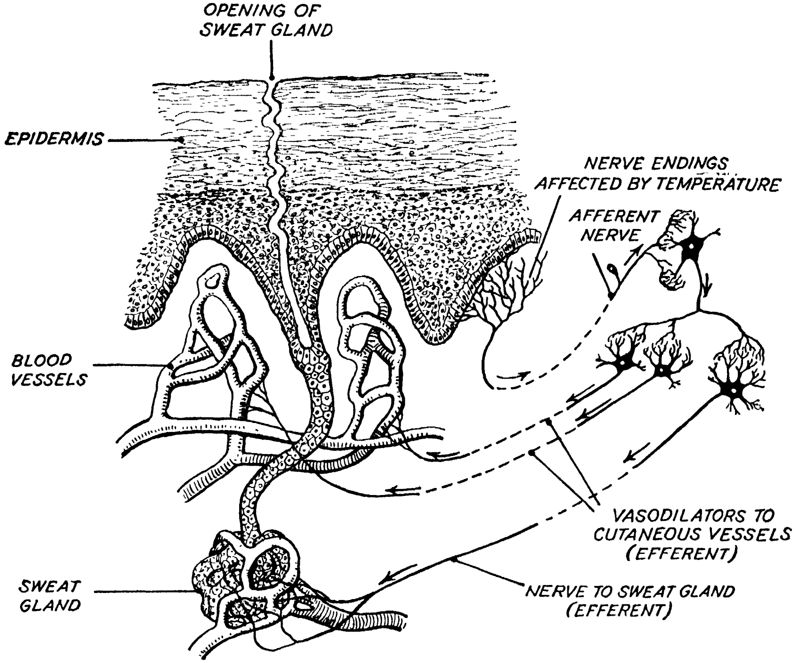


FIG. 61.—Diagram illustrating temperature regulation through nervous control of the sweat glands in the skin as described on page 119. (*Redrawn from Hough, Sedgwick, and Waddell "The Human Mechanism," Ginn and Company.*)

output, because this liquid is essential to the maintenance of the normal body temperature. Thus a person who is moderately active on a cold day will notice very little perspiration, but, when the temperature is high, the perspiration will be very abundant, and its continual evaporation will aid in keeping the body temperature at the normal level. When the excess water in the body fluids is not needed for temperature control, it is eliminated through the kidneys. Thus, if the water intake and body activity remain uniform, essentially the same amount of water will be given off from the body, but the proportion of the water that is excreted through the skin and through the kidneys will

show considerable variation depending upon environmental conditions. (Fig. 61.)

It is clear that the amount of sweat secreted depends upon the amount of blood that is permitted to flow through the capillaries surrounding the millions of sweat glands. This blood flow is under the control of the autonomic nervous system which, in an endeavor to conserve the body heat, constricts the blood vessels in the skin by inciting a contraction of the muscle tissue in the walls of the vessels. Under such conditions, comparatively little blood comes into contact with the sweat glands, and the materials removed are correspondingly less. Even under low temperature conditions, if a person suddenly engages in hard physical labor, the heat produced in the muscle tissues through the oxidation processes will tend to raise the body temperature. As a result the flow of blood to the skin will be augmented, secretion of sweat will be correspondingly increased, and the evaporation of the latter at the body surface will cool both the skin tissues and the blood flowing through them. Thus excretion through the skin is seen to be directly tied up with an essential body function; in the wisdom of the body a waste product on its way out is used to render an important service. Another instance of this has already been noted in the use of carbon dioxide to influence the respiratory center (page 80).

EXCRETION AND THE LUNGS

The aeration of the lungs by breathing supplies oxygen to the cells and at the same time removes the waste carbon dioxide and a relatively small amount of water from the blood. Breathing at the normal rate, 12 to 13 cu. ft. of carbon dioxide leave the body every 24 hours through the lungs, together with some 250 cc. of water in the form of vapor. Very minute, but often very noticeable, amounts of organic substances are also eliminated from the body by the outgoing air current. Adequate consideration of the functional activities of the lungs has already been given in the earlier chapter on Respiration (page 77).

EXCRETION AND THE LIVER

The association of the liver with excretion, as already noted in the previous chapter, is of primary importance. Thus the evidence indicates that the destruction of the discarded red corpuscles from the blood is to some extent a function of the Kupffer cells which take up an abode in the sinusoids of the liver where they are in a position to inspect the cellular elements floating slowly by in the blood stream. It is also evident that the spleen and the bone marrow share in the dismantling of the red cells; but at all events, the hepatic cells are

responsible for the formation and excretion of the unique excretory product, bilirubin, from the hemoglobin (page 100). But of even more importance is the fact that the liver cells collect the end products of protein metabolism from the blood stream and convert them into urea, which is excreted through the kidneys. It is interesting to note that the liver carries the bilirubin through its own bile ducts and deposits it in the intestine, but the urea is secreted into the blood stream for conveyance to the kidneys.

Since protein metabolism is essential for life, a great deal of attention has been given to the exceedingly complex chemistry associated with protein utilization in, and elimination from, the body. Even so, the story is still far from complete. Somewhat less than 90 per cent of the total nitrogen excreted leaves the body as urea. The remainder of the nitrogenous end products, containing some 10 to 15 per cent of the nitrogen released daily, is divided into several groups of compounds, notably uric acid, creatinine, hippuric acid, etc., some of which are well known, others essentially unknown. It can be said, however, that the synthesis of all the urea and of most of the other nitrogenous excretions is accomplished by the liver cells, working in association with various specific enzymes. To give one example, arginine, a split product of protein, is hydrolized in the liver by the action of the enzyme, arginase, to form urea and ornithine; the latter, still containing nitrogen, is subject to further disruptive enzyme actions in the liver, until the final excretion product, urea, is formed.

The important deaminization process in the liver should be considered in connection with the formation of urea. It will be remembered from the previous discussion that when an excess of amino acids occurs in the blood, the liver splits off the NH_2 fraction and converts the remainder of the amino acid molecule into the carbohydrate, glycogen, which may be used for fuel (page 57). The NH_2 group split off from the amino acid is further changed to ammonia (NH_3) and united with carbon dioxide to form urea and water, as shown by the equation: $2NH_3 + CO_2 = CO(NH_2)_2 + H_2O$.

EXCRETION AND THE KIDNEYS

The establishment of the triploblastic condition in animal organization marks the advent of a specialized excretory system which functions in the elimination of the nitrogenous cellular wastes from the organism. Possibly this new system is seen to best advantage in the development of paired segmental excretory tubes, the nephridia, in the earthworm. The nephridia lie in the coelomic cavity near the ventral body wall, through which they open to form a connection between

the coelomic cavity and the exterior. For the most part, the cellular wastes of the earthworm accumulate in the coelomic fluid which continuously bathes the tissues. The nephridia are so constructed that these wastes may be drawn into the lumen and carried to the exterior. Provision is also made for the collection of wastes from the blood stream through the vascularization of the nephridial walls. (Fig. 86.)

From a structural standpoint, the vertebrate excretory system can be regarded as an assemblage of great numbers of nephridia-like tubules to form a pair of definite excretory organs, the kidneys, which open by special ducts to the exterior. The study of the vertebrate excretory system is very interesting to the comparative anatomist because of the many homologies that are evident in the different groups. Three types of vertebrate kidneys are recognized, namely, the pronephros, mesonephros, and metanephros, the latter type being found in man and the higher vertebrates. Stated in essence, it may be said that the functional tubules of the pronephros open into the coelomic cavity; the mesonephric tubules generally lose their connection with the coelom and develop one with the vascular system; and the metanephric tubules are connected solely with the vascular system.

Human Kidneys.—The human kidneys consist of a pair of brownish-colored, bean-shaped bodies. They measure some 4 in. in length and about half that in breadth and lie well forward in the abdominal cavity, in contact with the dorsal body wall, one on each side of the mid-line as indicated by the near-by vertebral column. The long axis of each kidney lies in an anteroposterior direction, that is, parallel to the vertebral column, with the concave surface (hilus) turned inwards toward the median backbone. Like the other organs in the body cavity, the kidneys are enclosed in transparent capsules of peritoneal tissue. (Plate VI*A*.)

When cut in half lengthwise, three distinct areas of kidney tissue are noted. Outermost is a dense, faintly striated area, the cortex, which encloses a lighter colored and more extensive area, the medulla. Projections of the cortex toward the center serve to segregate the medullary tissues into cone-shaped pyramids. Each pyramid is oriented with its base in contact with the cortical tissue. Inwardly each pyramid terminates in a pointed secreting portion, the papilla, which opens into a third region, the pelvis. Connecting with the pelvis of each kidney is a large excretory duct, the ureter, which carries the urine to the bladder. The latter is a muscular-walled reservoir for the temporary storage of urine, secreted by the kidneys and brought to it by the ureters. An unpaired duct, the urethra, leads from the bladder to the external opening. The ureters, bladder,

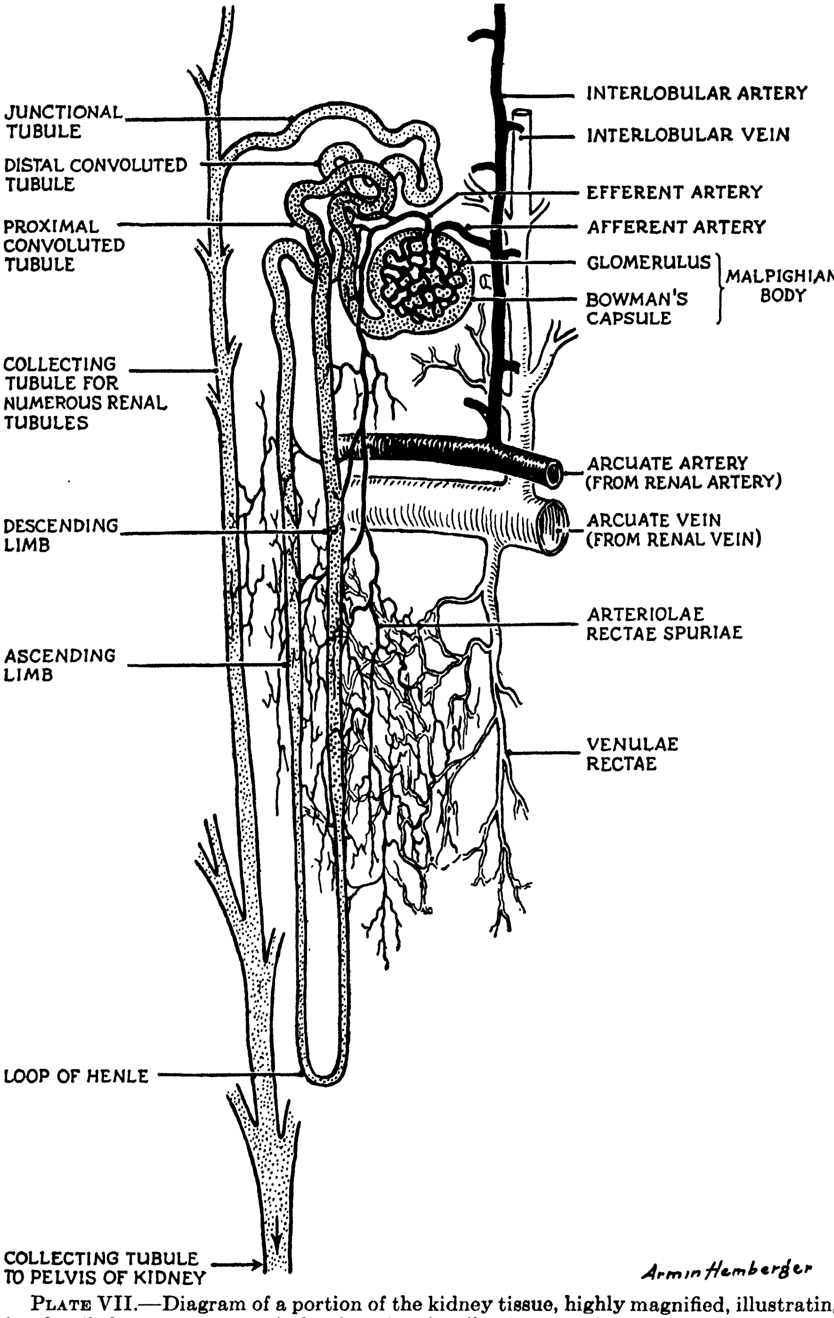


PLATE VII.—Diagram of a portion of the kidney tissue, highly magnified, illustrating the detailed arrangement of the functional collecting tubules and associated blood vessels.

and urethra do not function in the production of urine; they are solely concerned with its orderly elimination from the body. (Plate VI*B*.)

Histology of Kidney Tissue.—The functional elements, which compose the kidney tissue, are microscopic in size and consist of an enormous number of coiled renal tubules, each of which, originating in the cortex, follows a tortuous route before finally joining a common collecting tubule running to an opening in the papilla at the tip of one of the pyramids. Each renal tubule begins in the cortex with an enlarged terminal portion, the Malpighian body. The latter is roughly spherical in shape, has a double epithelial wall, Bowman's capsule, and contains a minute knot-like assemblage of thin-walled capillaries, the glomerulus, through which the blood continuously flows. The inner epithelial layer of the capsule is closely applied to the capillary walls. Wastes collected from the blood stream during its passage through the glomerulus diffuse through the capillary walls and epithelial lining and so enter the lumen of the renal tubule, en route to the pelvis. (Plate VII.)

But the Malpighian body with the glomerulus is not the only important functional part of a renal tubule. It has long been recognized that the renal tubule itself, particularly the convoluted proximal portion which terminates in the Malpighian body, is not merely a duct for the passage of the waste fluids but is active in forming the finished waste product, urine, secreted by the kidneys. Each renal tubule measures about ¾ in. in length; but with a diameter of only 0.0023 in., it makes so many turns and twists between the proximal portion in the cortex of the kidney and the distal end (junctional tubule) opening through a papilla into the pelvis that it is very difficult, if not impossible, to isolate a single tubule for direct experimentation. The walls of the proximal portions of the tubules contain a dense capillary network. (Plate VII.)

The circulation of the blood in the kidneys is as follows: blood reaches the kidney from the large renal artery. The latter subdivides to form the arcuate and interlobular vessels and, finally, forms the tiny afferent arteries which enter the glomerulus and give rise to the capillary network. After the blood has passed into and through the glomerular capillaries, it flows into the connecting efferent vessel. The latter, shortly after leaving the glomerulus, forms a capillary network in the walls of the proximal convoluted tubule. Thus the blood, which has just passed through the glomerulus and been freed from the wastes, passes next to the epithelial cells in the walls of the renal tubules. Blood passing through the kidney is conducted away from the tubules by a series of veins (venulae rectae, interlobular, and

arcuate) leading to the renal vein. This circulation of the blood through both the glomeruli and the proximal portion of the tubules in succession is very important because it permits the reabsorption of certain constituents of the glomerular wastes, as will be seen in the following section when the functional features of the kidney are considered.

Kidney Functions.—From the blood flowing through the kidney tissues about 50 oz., or, roughly, 2½ pt., of the composite waste product urine is removed each day and passed from the body. The amount of urine excreted, however, is subject to wide variation, from a minimum amount of approximately 1 pt. to as much as 5 pt. As shown above, this variation in urine secretion is associated with temperature control: the more water leaving the body through the sweat glands the less will leave in the urine (page 120). Under uniform temperature conditions the amount of urine excreted can be markedly increased by drinking more water, particularly if it contains certain soluble substances, diuretics, which tend to increase kidney activity. Examples of diuretics are found in various salts and such substances as digitalis, caffeine, and urea. (Fig. 62.)

A chemical analysis of human urine shows that it typically consists of approximately 96 per cent water; 1.8 per cent inorganic salts, pigments, and obscure nitrogen compounds; and 2.2 per cent urea, this last substance being the principal end-product of the complicated protein metabolism that began with the intake of the nitrogen-containing foods. All of these solids are carried in solution in the water so that the specific gravity of urine (1.020) is slightly above that of pure water. We have noted in the previous chapter that the chemical changes necessary to convert the protein wastes of the cells into urea and certain other less known nitrogenous compounds occur in the liver, the kidney acting only in the removal of urea from the blood (page 100). Urea itself is a soluble crystalline substance whose chemical nature was determined over a century ago. It was the first organic substance to be synthesized in the laboratory. This was accomplished in 1828 by Wohler from an inorganic compound containing the elements carbon, hydrogen, oxygen, and nitrogen of which urea is composed.

It is comparatively easy to analyze urine and find the percentages of urea, water, and other substances present in this complex waste product, but the problem of determining how it "got that way" in the kidneys has proved to be very difficult, and it is still the subject of controversy and extensive investigation by the research workers in this field. The questions at issue center primarily around the

SOURCES OF LOSS AND GAIN TO THE BLOOD.

A. SOURCES OF LOSS:—

I. *Loss of Matter.*

1. The lungs: carbonic acid and water (fairly constant).
2. The kidneys: urea, water, salines (fairly constant).
3. The skin: water, salines (fairly constant).
4. The tissues: constructive material (variable especially in the case of those tissues whose activity is intermittent, such as the muscles, many secreting glands, &c.), water, &c., to form lymph.

II. *Loss of Heat.*

1. The skin.
2. The lungs.
3. The excretions by the kidney and the alimentary canal.

B. SOURCES OF GAIN:—

I. *Gain of Matter.*

1. The lungs: oxygen (fairly constant).
2. The alimentary canal: food (variable).
3. The tissues: products of their activity, waste matters (always going on but varying according to the activity of the several tissues).
4. The lymphatics: lymph (always going on but varying according to the activity of the several tissues).

II. *Gain of Heat.*

1. The tissues generally, especially the more active ones, such as the muscles.
2. The blood itself, probably to a very small extent.

FIG. 62.—Table illustrating the sources of loss and gain to the blood. "One must be careful not to confuse the losses and gains of the blood with the losses and gains of the body as a whole. The two differ in much the same way as the internal commerce of a country differs from its import and export trade." (*Huxley—Barcroft.*)

determination of the specific functions of the Malpighian bodies in comparison with those of the vascularized renal tubules. Does the glomerulus in a Malpighian body act merely as a mechanical filter in removing waste substances from the blood? Or is there a selective action so that only the excess water and salts are removed from the blood in the glomeruli, the other wastes found in the urine, including urea, being added by the secretory activities of the epithelial cells in the walls of the renal tubules?

Very ingenious and difficult experiments have made it possible to remove for analysis some of the fluid given off in the microscopic glomeruli of the frog's kidney. Such analyses show that the glomerular fluid in the frog is basically the same as urine, with all constituent substances present but in a very diluted form. For example, it is found that the concentration of urea in urine is about one hundred times greater than it is in the glomerular fluid. Glucose, however, is present in the glomerular fluid but is entirely absent from normal urine, and also various inorganic salts, notably sodium chloride, present in the glomerular fluids do not show a constant relationship to the amounts present in the urine. These so-called threshold substances are considered below.

It seems clear from these experiments that, with the exception of glucose, the glomeruli filter off a liquid from the blood that may be regarded as essentially a very dilute urine. As a matter of fact, the evidence indicates that about the only substances carried in solution in the blood that are not permitted to pass through the walls of the glomeruli are the normal blood proteins. This is a remarkable feature because it can be shown that when foreign proteins are present in the blood, they will be quickly excreted by the kidneys. Finally, experiments show that the amount of fluid removed from the blood by the glomeruli varies directly with the blood pressure and with the amount of blood going through the kidney, which indicates that, to some extent at least, the glomeruli act as mechanical filters.

The glomerular fluid passes from each glomerulus to the lumen of the proximal portion of the renal tubule, the walls of which, it will be remembered, are highly vascularized and the vessels so connected that the blood leaving the glomeruli comes next to the tubules. This arrangement makes it possible for the epithelial cells lining the tubules to absorb water and salts from the glomerular fluid and to return them to the blood stream in such quantities as will keep the blood plasma at normal levels, also under normal conditions to absorb all the glucose and return it to the blood stream. Evidence exists also, in certain cases, of a secretory activity in the tubules. If such action occurs, it

means that the cells of the tubules absorb waste substances directly from the blood stream and add them to the glomerular fluid for excretion. Probably both absorption and secretion of materials in the glomerular fluid can take place in the renal tubules, but the concensus of opinion is that the main function of the tubules is absorption.

The fact that the kidneys can excrete urine, which may vary in the percentage of water and solids present, enables them to act as a regulator of body fluids. When perspiration is abundant, the amount of water excreted from the body by the kidneys is reduced. This is due to the fact that the cells in the kidney tubules absorb water from the dilute glomerular fluid and return it to the blood stream for elimination through the sweat glands of the skin as an aid in maintaining a uniform body temperature. If the external temperature and the muscular activity combined should be sufficient to endanger the normal water content of blood plasma through excessive perspiration, the kidneys will return a large percentage of water back to the blood, and the small amount of urine excreted will be correspondingly concentrated. If, in spite of profuse perspiration, the body temperature rises even slightly above normal levels under conditions of excessive heat and activity, perspiration may suddenly decrease. If this occurs, the body temperature will quickly rise, and the victim will be prostrated by the heat, the so-called "sunstroke" and a serious condition.

Not only is the normal water-plasma relationship of the blood maintained by the selective absorption of materials from the glomerular fluid through the action of the kidney tubules, but also the salt reserve in the blood, particularly sodium chloride, is controlled in the same way. Excessive amounts of salt in the diet will be absorbed by the blood stream and then quickly eliminated through the kidneys. However, the exact amount of salt appearing in the urine at any time will depend upon the needs of the blood plasma. Thus, to consider perspiration once more, it is found that the amount of salt released from the body in sweat may be very large if perspiration is profuse. In such conditions, the cells of the kidney tubules endeavor to absorb a sufficient amount of salt from the glomerular fluid to replace that lost from the blood by perspiration. Authorities have recently called attention to the serious depletion of salt in the body as the result of excessive perspiration. They have advised factory employees working under high-temperature conditions that additional supplies of salt should be taken with the food or with the drinking water. (Fig. 61.)

Finally, the glomerular filtrate contains an appreciable amount of glucose in solution. None of this appears in the urine excreted from normal kidneys; it is all absorbed by the tubules and returned to the

blood stream. In diabetes, the amount of sugar in the blood is greatly increased, with the result that the glomerular fluid has an abnormal sugar content. In such cases, the tubules do not or cannot reabsorb all of the sugar found in the glomerular fluid and return it to the blood stream, and so some of it is excreted in the urine. The excess of sugar in the blood of the diabetic will intensify his thirst so that abnormal amounts of water will be drunk which will, in turn, cause excessive urination. Also, some of the excess fluids may gradually accumulate in the tissues, thus producing an edematous condition (page 104).

But the functional kidney cannot be regarded solely as a filtering and absorbing organ, for it is well known that important chemical reactions, both synthetic and analytic, occur in its tissues. One of the most important of these reactions is concerned with the splitting of urea to form ammonia and carbon dioxide when the acidity of the urine tends to become abnormally high. Such a condition may occur when an excess of animal tissues is eaten or when certain inorganic acids are taken into the alimentary tract. The ammonia thus formed from urea is combined with the acid to form a salt, and the excessive acidity of the urine thereby reduced. The reverse of this process, if it occurs, would increase the acidity of the urine when it tended to be too alkaline. The latter condition is possible when there is a great excess of plant foods in the diet. Since, however, urine may vary from a markedly acid condition (pH 4.82) to an alkaline one (pH 7.45) with a normal slightly acid condition (pH 6) it is necessary only that the chemical reactions in the kidney cells, as just described, be performed when the normally wide limits in either direction are passed. The upshot of the whole matter is, of course, as emphasized above, that varying the acidity of the secreted urine permits the maintenance of an essentially constant (pH) level in the blood plasma and in the body tissues.

Another demonstrated case of synthesis by the kidney cells is the formation of hippuric acid, which is a prominent constituent of the urine of herbivorous animals and also of man when the diet consists largely of plant tissues. The latter contain a considerable quantity of benzoic acid, which is absorbed from the digestive tract and must be excreted. The kidney cells are able to combine the benzoic acid with glycine, one of the amino acids, and thus form hippuric acid which is secreted in the urine.

The complex and somewhat variable liquid product of the kidneys, urine—collected in very minute amounts by the individual renal tubules—leaves each kidney at the rate of about one drop per minute and flows through the ureter to the bladder. It is propelled through

the ureter partly by gravity, especially when standing, and partly by peristalsis in the walls of the ureter. The peristaltic waves are stated to occur every 10 to 20 seconds and to travel toward the bladder at a rate in excess of ½ in. per minute. Since the ureter in man is in excess of 1 ft. long, it probably takes from 15 to 20 minutes for a drop of urine to travel this distance. It is possible for the urologist to insert an apparatus with an electric bulb up the urethra and thus to illuminate the interior of the bladder to determine the normality of the urine secretion from each kidney. (Plate VI*A*.)

The urine is retained in the bladder until a considerable amount, about ½ pt., has accumulated. This retention is accomplished by a muscular valve, the internal sphincter on the urethra, which is normally in a state of contraction and so prevents the release of the urine to the exterior until desired. The continual accumulation of the urine in the bladder sets up a nerve stimulation when it reaches a certain point, giving the sensation of fullness. Considerable latitude is allowed in responding to the sensation. If urination is voluntarily delayed, the bladder muscles relax somewhat, and no further sensations are noted until considerable more urine has accumulated, when the sensation is again set up with added force. Urination (micturition) is accomplished by the contraction of the muscular tissue in the bladder walls synchronously with the relaxation of the internal sphincter. Also, additional pressure on the bladder is caused by the contraction of the muscles in the abdominal wall, with the glottis closed. Urination, though essentially automatic or reflex in nature, is also under voluntary control, as evidenced by the fact that the process may be delayed, stopped, or started.

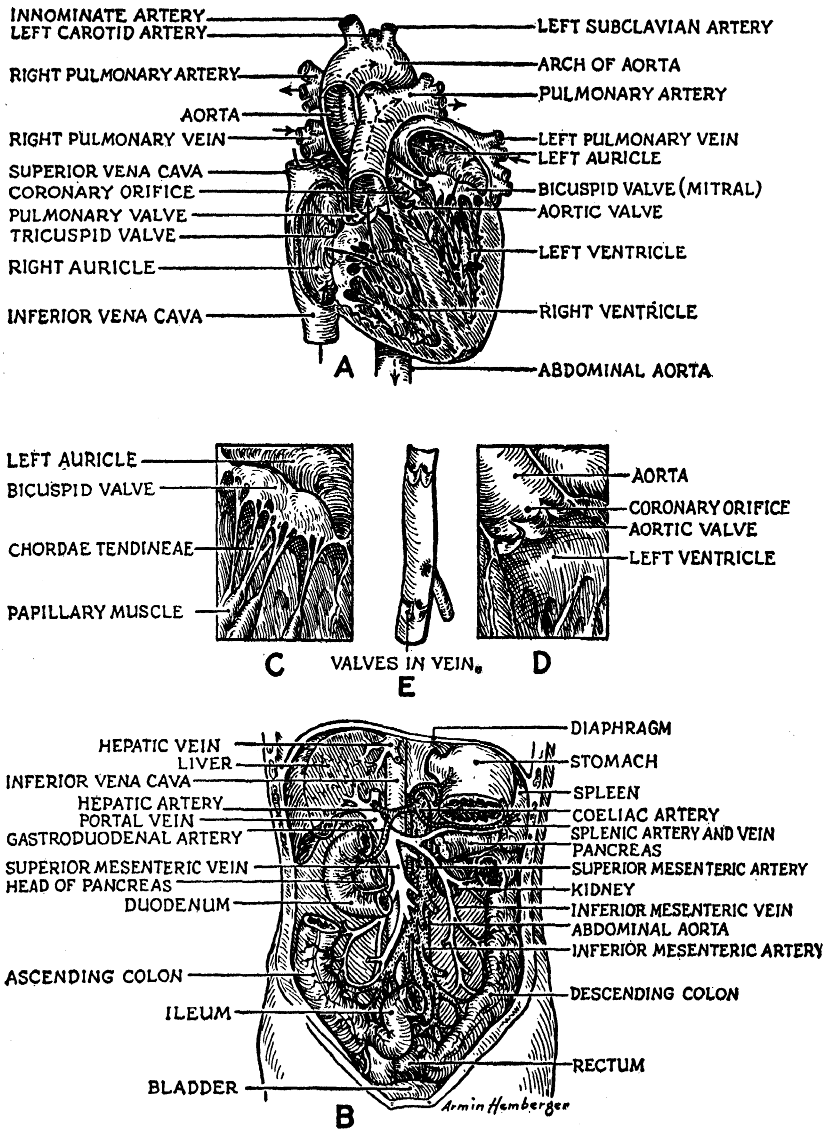


PLATE VIII.—Drawings illustrating various structures associated with the human vascular system. Semidiagrammatic. *A*, internal structure of the heart, ventral view; *B*, chief vessels of the abdominal viscera; *C*, bicuspid valve; *D*, coronary orifice in aorta; *E*, valves in vein.

CHAPTER VII

THE BIOLOGY OF THE VASCULAR SYSTEM

It is evident from the previous chapters that the essential functions of nutrition, respiration, secretion, and excretion in the highly developed human organism are dependent upon the vascular system for the transportation of an amazing array of substances. But even more important than this is the basic fact that every cell in the body is dependent upon the vascular system for bringing to it a continuous supply of essential materials and for removing the cellular wastes. The vascular system is equipped to render this universal transportation

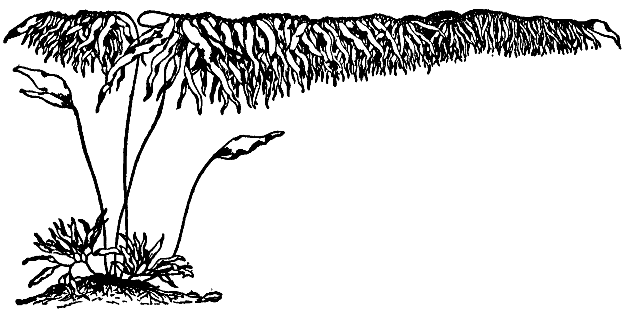


Fig. 63.—The Giant Kelp, a marine Alga. (*Woodruff, after Ganong.*)

service in the body through an infinitude of tubular vessels, large, small, microscopic; associated open spaces in the tissues; a liquid river of life, the blood; and an efficient automatic pump, ~~the heart, which forces~~ the blood through the designated channels.

In the less highly differentiated organisms the problems of transportation are solved in a much simpler fashion by the direct transfer of materials from cell to cell. An aquatic environment is of great assistance in these forms of life, for, when the outer surface of a cell is in contact with the water, the interchange of respiratory gases and liquid wastes is greatly aided. Thus in the Algae, which includes a large group of comparatively simple water plants in which the cellular differentiation is not marked, plant bodies of varying size reach their climax in the enormous marine kelps. The kelps may attain a length of 200 ft., with no special provision for the transportation of materials throughout the plant body. Furthermore, plants like the mosses,

which live outside the water and have no conducting tissues, are always very small in size because they are unable to conduct essential materials from the soil more than a short distance above the surface of the ground. The higher types of soil-living plant, such as the ferns and seed plants, which have developed specialized vascular tissues, grow to considerable heights because of their ability to transport essential materials from the roots and leaves to all regions of the plant body as required. (Figs. 63 to 65.)

In animals, cellular differentiation is, generally speaking, more advanced than in plants. Even so, in the smaller, aquatic forms with a minimum of

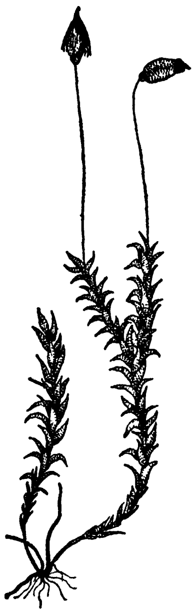


FIG. 64.

FIG. 65.

FIG. 64.—The plant body of a typical moss. × 1. (*Woodruff, after Ganong.*)
FIG. 65.—The plant body of a common fern. × $\frac{1}{10}$. (*Woodruff, after Ganong.*)

cellular differentiation, the cells of the organism are able to supply their needs without the aid of a vascular system. Some of the Coelenterates attain considerable size, as, for example, certain jellyfish, but the low degree of cellular differentiation and the aquatic environment solve the transportation problems unaided by any special vascular tissues. On the other hand, much smaller aquatic animals, as in various species of tropical fish, require a differentiated vascular system because the highly specialized cells of these organisms are not able to look after the transference of materials from cell to cell. (Fig. 66.)

Variations in the degree of development of the vascular systems of the land-dwelling animals are closely associated with the need for

oxygen transportation. Thus the vascular system of the relatively simple earthworm is found to be very complete and highly organized, whereas in the much more advanced insect group the opposite is true. This latter condition is directly associated with the ability of the insects to transport oxygen to the cells by a unique system of air tubes. The latter form a remarkably complete network throughout the tissues, and thus the oxygen reaches the cells without the intervention of the blood stream. Accordingly the insect vascular system, relieved of the basic duty of carrying a constant supply of oxygen to the cells, does not attain the high estate characteristic of less differentiated animal types in which this duty is paramount. (Fig. 40.)

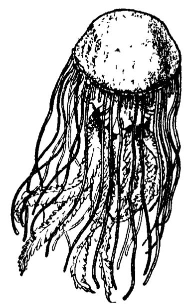


Fig. 66.—A marine jellyfish, some species of which attain a diameter of three feet or more. (*Hegner.*)

STRUCTURAL FEATURES ASSOCIATED WITH THE VASCULAR SYSTEM

The vertebrate system consists of (1) a network of tubular vessels associated with (2) open channels and tissue spaces through which (3) a liquid medium, the blood, circulates throughout the body by the action of the pump-like heart. The vessels of the body are divided into arteries, which carry blood away from the heart; veins, which carry blood to the heart; capillaries, which connect the arteries and veins in the tissues through an elaborate system of microscopic tubes; and the heart, which is a highly modified blood vessel adapted for pumping blood. Blood leaving the heart must make a complete circuit involving a connected system of arteries, capillaries, and veins before it again reaches the heart. In addition to the closed tubular system, there is an open vascular system consisting of various-sized spaces, or sinuses, in the tissues, together with definite lymph vessels having extremely thin walls, through which a fluid derivative of the blood, the lymph, slowly moves. Lymph is the circulating medium that comes into contact with the individual cells so that this tissue fluid stands as the final agent in the actual transfer of materials to and from the cells. However, in the sinusoids of the liver and certain other organs the blood, rather than the lymph, is in direct contact with the individual cells. (Fig. 54.)

Blood

Blood Plasma.—Blood may be regarded as a liquid tissue, that is, a tissue in which the intercellular material is liquid rather than solid. In the other tissues of the body, the intercellular material is more or

less solid and therefore holds the cells rigidly in place. The liquid intercellular material of blood, the blood plasma, is a highly complex medium and marvelously adapted for the transportation of the essential materials. Since the blood plasma is continually receiving an almost infinite variety of materials from the cells, its exact chemical composition varies continuously, and so an exact analysis can never be obtained. In addition, blood plasma is equipped with a very important mechanism that results in the coagulation, or clotting, of blood when necessary to stop bleeding. Finally, floating in the plasma are enormous numbers of very highly specialized blood cells, the red and white corpuscles, which are important agents in various blood functions as will be indicated later.

Blood plasma, since it has a number of solids dissolved in it, is not only figuratively but literally thicker than water, with a specific gravity around 1.005. Of the total weight of the body, it is estimated that from 5 to 7.5 per cent consists of blood. In the adult weighing 150 to 160 lb., this would mean in the neighborhood of 6 qt. of blood. Of this total, it is believed that approximately one-fourth is normally present in the lungs, major blood vessels, and heart; one-fourth in the liver; one-fourth in the voluntary muscles; and the remainder in the various other organs and tissues of the body. If normal blood is centrifuged, it will be found that the cellular elements will be separated from the plasma and thrown to the bottom of the centrifuge tube. This shows, of course, that they are heavier than the plasma. If the relative amounts of plasma and blood cells are determined after centrifuging, it will be found that the plasma constitutes about 54 per cent, and the cells 46 per cent of the whole blood.

Blood plasma consists of about 92 per cent water and 8 per cent solids in solution; and, in addition in every 100 parts of plasma is dissolved between 60 and 70 parts of the gases, oxygen, carbon dioxide, and nitrogen. The exact amount of the dissolved gases varies in different animals and in different individuals, and also a marked difference exists between the venous blood returned to the lungs from the tissues and the arterial blood sent from the lungs after aeration. It should be understood that, generally speaking, the blood gases are carried in chemical compounds (page 160). An approximate compar-

Blood	Oxygen, per cent	Carbon dioxide, per cent	Nitrogen, per cent
Arterial	19.4	49.7	1.6
Venous	14.0	54.6	1.6

ison between arterial and venous blood gases is given in the table on page 136.

The inert nitrogen, it will be noted, goes through the tissues unchanged, but the oxygen is decreased and the carbon dioxide increased in the plasma as the blood moves through the body tissues. This is, of course, due to the demands of the cells for respiratory processes, as has been noted in a previous chapter (page 79).

The complexity of blood plasma is due in part to the many products associated with cellular activities that it carries in solution and in part to certain characteristic compounds of its own. These latter consist of three soluble blood proteins designated as *fibrinogen*, *serum-globulin*, and *serum-albumin* which, together, total around 7 per cent of the solids. Fibrinogen is directly concerned with the coagulation of blood. During this process, fibrinogen is changed from a soluble to an insoluble protein which precipitates in the plasma as needle-shaped crystals (Fig. 82). When the plasma clots, a liquid, the blood serum, is gradually squeezed out; it will not clot again, as the fibrinogen has been used up. The serum-globulin and serum-albumin are typical natural proteins and, like the proteins in general, so complex that the molecular structure has never been established. The chemical analysis of serum-albumin shows that it consists of approximately 53 per cent carbon, 7 per cent hydrogen, 16 per cent nitrogen, 2 per cent sulphur, and 22 per cent oxygen, with the formula given as $C_{78}H_{122}N_{20}SO_{24}$. The function of fibrinogen, as noted, has been fully established, but the functions of the other two blood proteins are still obscure. For one thing, it is certain that they are responsible for the osmotic pressure that tends to draw water into the blood vessels. Their great importance is indicated experimentally by the fact that, when the normal amounts of blood proteins present in the blood plasma are reduced experimentally, a rapid restoration to normal takes place as quickly as possible.

Cells of the Blood.—The blood corpuscles comprise two main types of living cells; the red corpuscles, or erythrocytes; and the white corpuscles, or leucocytes. The former are so named because they contain the red respiratory pigment hemoglobin, which is necessary for the transportation of oxygen from the lungs to the tissue cells, as described in the earlier section on Respiration. The human erythrocytes may be described as tiny, biconcave discs with a diameter of about 0.0003 in. and not over one-fourth of this in thickness. The mature erythrocyte does not show a differentiation into nucleus and cytoplasm. From the dimensions given, it can be calculated that more than 10 million of the red cells can be placed side by side in 1 sq.

in. of space. In blood freshly drawn from the vessels, there is a tendency for the corpuscles to adhere to each other to form long rolls (rouleaux) like stacks of coins. Microscopic observations on corpuscles flowing through tiny capillaries, for example, in the web of the frog's foot, show that the cytoplasmic body of the erythrocyte is soft and flexible, so that the normal shape is easily modified when necessary in order to pass through a tiny capillary. Blood contains an enormous number of erythrocytes at all times. In the male there are normally about 5,000,000 per cubic millimeter of blood and about 10 per cent less or 4,500,000 per cubic millimeter, in the female. (Fig. 67.)

The erythrocyte consists of a ground substance, or stroma, in which the hemoglobin is suspended; the latter probably comprises about 35 per cent of the total weight. The hemoglobin may be separated from the stroma and drawn into the plasma by hemolytic

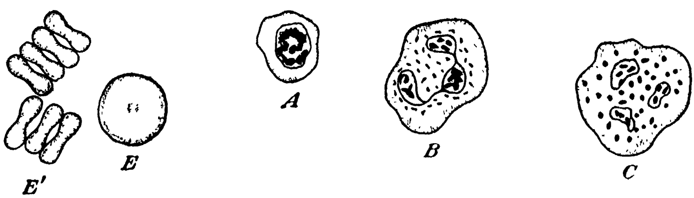


FIG. 67.—Sketches showing various types of blood cells. *E*, red blood cell (erythrocyte); *E'*, stacking of red blood cells (rouleaux); *A*, *B*, and *C*, types of white blood cells (leucocytes). (*Watkeys, Daggs.*)

action, and then the stroma is seen as a colorless body. Hemolysis occurs when the membranes of the red cells are ruptured by mechanical means, such as freezing or thawing, or when they are placed in a hypotonic liquid, such as distilled water. The latter gradually penetrates the membrane and diffuses through the cytoplasm. Finally, the membrane ruptures from the increased internal pressure, and then the enclosed hemoglobin flows out into the surrounding liquid. If red cells are placed in a hypertonic medium, the reverse process will occur with a movement of liquid from the cell into the surrounding medium. In this condition the cell membrane will become wrinkled (crenation) as more and more of the fluids leave the cell body. If the corpuscles are put into an isotonic fluid, that is, one that has the same osmotic pressure as normal blood plasma, no abnormal loss of materials occurs through the cell wall, and the cells will remain unchanged. It is sometimes necessary, following accident or disease, to inject isotonic fluids into the tissues or even directly into the blood stream. Two important isotonic fluids are 0.9 per cent sodium chloride and 5 per cent dextrose.

The leucocytes are colorless cells and, for the most part, amoeboid. It is clear that one of their chief functions is to ingest, or phagocytize, invading parasites and thus control infection. Many other functions have been suggested, but the evidence is not conclusive. The normal number of leucocytes in the blood is much less than the number of red cells, and it is subject to wider variation. The number commonly found varies from 6,000 to 10,000 per cubic millimeter. Thus only one leucocyte is present in the blood for some 500 to 800 red cells. Morphological studies on the leucocytes, based largely on staining reactions, show that there are several different types. For our purposes, we may recognize two main groups; the nongranular leucocytes and the granular leucocytes. The latter comprise about 75 per cent of all leucocytes and are characterized by a granular cytoplasm and a nucleus consisting of several distinct lobes. They are very important in the control of invading microorganisms because they are actively phagocytic. Mention should also be made of another cellular element, the blood platelets, which are known to be an important factor in the coagulation of blood. The platelets are extraordinarily minute, measuring only about 0.00012 in. in diameter, but they are considerably more numerous than the white cells, approximately 250,000 per cubic millimeter.

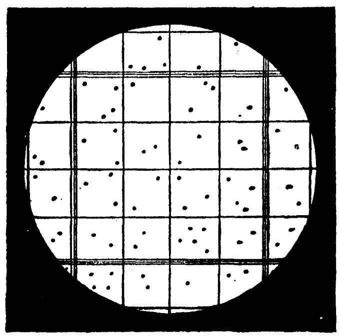


FIG. 68.—Diagram illustrating methods used in blood counts. A special ruled slide for microscopic observation is used. Cells are counted in the sixteen squares enclosed within the triple lines: an area which represents 1/200th cubic millimeters of blood. (*Smith, "Exploring Biology," Harcourt, Brace & Company, Inc.*)

Blood Counts.—For the diagnosis of various diseases, the blood count gives important evidence. This is accomplished by securing a small amount of blood from the patient, diluting it with isotonic salt solution, and then placing a measured amount of the diluted blood in a counting chamber for microscopic observation. The counting chamber is divided into numerous standard units so that, by counting the number of blood cells in several units and averaging the separate counts, a fairly accurate determination of the number can be made. Thus, in the case of anemia, the number of red cells may be abnormally low, or the abnormal condition may be due to a lack of hemoglobin in the individual cells. Both conditions can be determined with considerable accuracy. On the other hand, the number of red cells may be greatly increased without harm. People who live in high altitudes normally have increased numbers of the red cells to compen-

sate for the reduced oxygen pressure. A temporary increase in the count usually follows vigorous exercise. Concerned with the increase in the red cells is the red marrow of the bones in which they are developed and the spleen where they are temporarily stored until needed. In the case of severe bleeding following injury, tremendous quantities of these oxygen carriers may be quickly supplied from the reserves in the spleen. (Fig. 68; page 212.)

The white blood cell count is very important in diagnosing the development of an infection in the body tissues. If the infection is severe, the increase in the white blood cells, as revealed in successive counts extending over several hours, may be very marked, and, in general, the severity of an infection can be gaged by the variations in the white blood cell count from normal levels. Under certain conditions, it may be necessary to make a differential blood count in order to determine the relative numbers of the various types of white blood cell present.

Blood Channels

The Heart.—With the nature of the circulating fluid in mind, attention may next be directed to the main features of the tubular

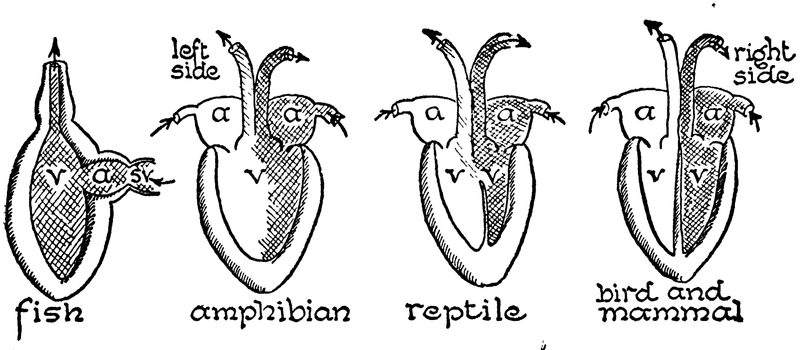


Fig. 69.—Diagrams illustrating internal structure of various types of vertebrate hearts from the two-chambered (fish) to the four-chambered (bird and mammal). *a*, auricle; *sv*, sinus venosus; *v*, ventricle. (*Hunter, Walter, and Hunter, "Biology," American Book Company.*)

channels through which blood passes in its continuous and rapid circulation through the body. The center of this distributing mechanism is a highly modified blood vessel, the heart, which from the earliest stages of embryonic development to the last moment of life maintains a continuous rhythmic beat and thus forces the essential life fluid to all parts of the body so that every cell may carry on the essential interchange of materials.

The heart in the various classes of vertebrates shows considerable anatomical variation. In the lowest fish-like forms, it is essentially a portion of the venous system consisting of a receiving chamber, the auricle, and a pumping chamber, the ventricle. Blood pours into the auricle from all the body tissues and is passed into the ventricle. The contraction of the latter drives the blood with sufficient power to force it through the gills for oxygenation, then through the body tissues and, finally, to return it once more to the auricle. In a somewhat higher air-breathing vertebrate, like the frog, the heart seems to be in a transitional, and possibly rather unsatisfactory, stage with three chambers: right auricle, left auricle, and common ventricle. There is the possibility in the three-chambered heart of mixing, in the ventricle, the venous body blood and the freshly oxygenated blood returned to the left auricle from the lungs and skin. As a matter of fact, the internal structural arrangements in the frog's heart reduce the possibility of mixing arterial and venous blood to a minimum. (Fig. 69.)

Anatomically the human heart does not bulk very large in the total weight of the body. Nor is it very impressive when it is dissected and found to consist largely of what appears to be a rather primitive type of muscular tissue, the cardiac tissue, associated with some flabby looking valves and a minimum of connective tissue elements for support. Further dissection, however, reveals the presence of an elaborate, but obscure, neuromuscular apparatus for general control of the cardiac tissues. The apparent simplicity of heart structure gives no indication of the amazing functional ability that this organ possesses, for it is one of the most noteworthy and efficient organs to be found in the entire range of protoplasmic organization. The ability to contract rhythmically and continuously—even a moment's cessation spells unconsciousness—throughout the life span is an inherent property of the cardiac muscle tissue. Rhythmic contraction is initiated in the early embryo without the aid of the nervous system, and it remains basically independent throughout life, though the rate of contraction may be varied within certain limits in accordance with bodily needs and conditions. (Fig. 79.)

In the four-chambered heart, present in man and the higher vertebrates, are two blood-receiving chambers (right and left auricles) and two blood-dispatching chambers (right and left ventricles) with a complete separation between the right and left sides. Thus the blood, to get from the left side of the heart to the right side, must leave by way of the aorta from the left ventricle, pass through the capillary network in some body tissue, and finally return to the right auricle through the venous system. In passing from the right to the

left side of the heart, the blood must leave by way of the pulmonary artery from the right ventricle, pass through the capillaries in the lungs, and return to the left auricle through the pulmonary veins. (Fig. 70.)

Possibly one of the most striking examples of widely different hearts may be found in comparing the heart of the elephant with that of the tiny hummingbird. The heart of the elephant weighs 48½ lb., and beats only a few times per minute, whereas that of the humming bird weighs 0.01 oz. and beats at the amazing rate of some 2,000 times per minute. Large or small, fast or slow, the heart never deviates from its sole function—driving blood through the branches of the vascular system, near and far, so that the needs of the individual cells may be supplied from the blood stream.

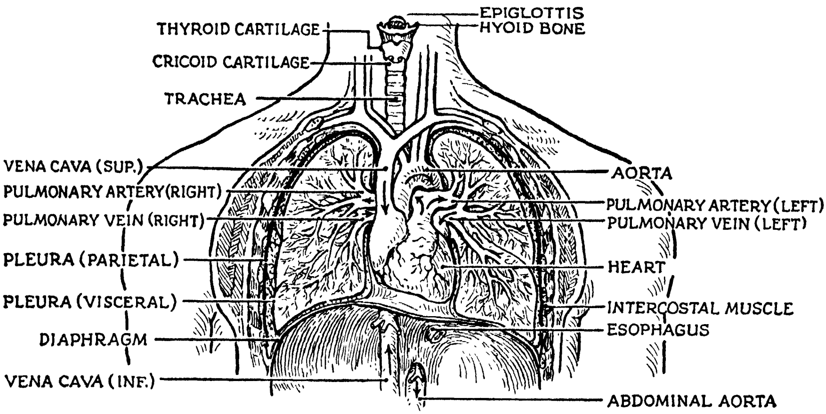


FIG. 70.—Drawing showing the general position and structure of the heart and the course of the blood in the main vessels.

The human heart is conical in shape and about the same size as the closed fist. The average measurements, therefore, are around 4.75 in. long by 3.5 in. wide. The four chambers are about equal in their liquid capacity which amounts to about 5 cu. in. The heart lies between the right and left lungs so that it is not seen, when the ventral wall of the chest is removed, until the lungs are pulled aside. In its normal position, the base of the heart, to which the large connecting vessels are attached, lies roughly beneath the median sternum of the chest wall, and the apex of the heart is situated below and well to the left side of the thorax, ending between the fifth and sixth ribs. The relative positions (but not the relative sizes) of the large blood vessels which connect the heart at the base, as seen from a ventral view, may be visualized by comparing them with the digits of the right hand, partially closed, palm down. In this comparison of

position, the thumb and first finger are comparable to the inferior and superior *venae cavae*, respectively; the second finger, to the aorta; the third finger, to the pulmonary artery; and the fourth finger to the pulmonary veins returning the blood to the left auricle. (Fig. 71.)

Histologically, the heart is largely composed of special cardiac muscle tissue. But there is a basic three-layered arrangement of the heart tissues, as in the case in the arteries and veins. The lining, or endocardium, of the heart is a thin layer of endothelium which is continuous with the lining of the other blood vessels, as noted below. External to the endocardium is the middle layer, or myocardium. The latter is by far the thickest layer in the heart wall and consists

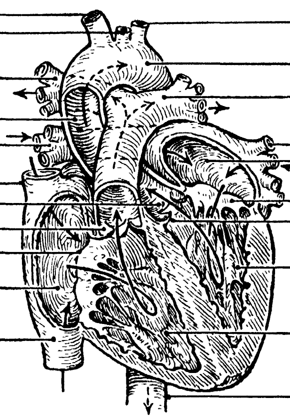


FIG. 71.—Drawing illustrating the internal anatomy of the human heart. Arrows indicate the direction of the blood flow into, through, and out of the various chambers of the heart.

of cardiac muscle tissue with a minimum amount of connective tissue for the support and attachment of muscle fibers. The third layer, the epicardium, encloses the heart. The epicardium is really double-walled; the inner layer, lying next to the myocardium, is separated from the outer layer by the pericardial space which contains pericardial fluid. (Fig. 12.)

Between the auricle and the ventricle on each side of the heart is an important valve. On the right side of the heart, the valve is known as the *tricuspid* and, on the left side, as the *bicuspid*. Both valves have essentially the same construction and consist of a sheet of connective tissue, covered above and below with endocardium, and lying between the auricle and ventricle at right angles to the longitudinal axis of the heart wall. This transverse sheet of valvular tissue may be thought of as being perforated in the center so that the flaps hang down into the ventricle when the valve is open. The tip of each

flap is attached to ligamentous threads which are connected with the ventricular wall. When the auricle contracts, the flaps are relaxed and hang down into the cavity of the ventricle, thus leaving a central opening for the passage of blood from auricle into ventricle; when the ventricle contracts, the flaps are pushed up toward the auricle by the blood pressure until the opening is closed. They are kept in the proper position to close the opening by the attached ligaments. (Figs. 72, 77.)

Arteries.—The arteries are strong, muscular walled tubes with a great deal of elasticity. The latter quality exists largely as a result of an abundant supply of elastic tissue intermingled in the cardiac tissue of the walls (page 27). The arteries need to be strong because they are continually under pressure from the blood which is forced

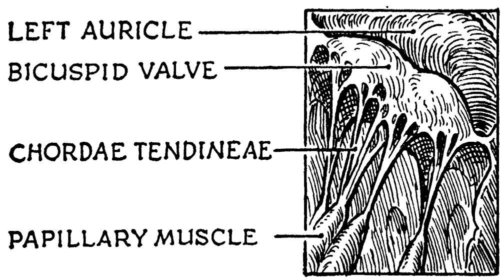


FIG. 72.—Drawing illustrating the finer structure of the heart valves. *Cf.* Figs. 71 and 77.

out by the contraction of the ventricles, and they need to be elastic to compensate in some degree for the additional blood forced into them by the heart action, so that a uniform blood pressure may be maintained. Expanding with the heart contraction, the arteries gradually contract during diastole. The result is that an essentially uniform flow of blood is maintained instead of a decidedly irregular one. Even so, it is always possible to detect the additional blood in an artery, following each ventricular contraction, by the wave of expansion that, beginning in the aorta, rapidly moves along the arterial network. This arterial expansion is spoken of as the *pulse;* and when the artery is located near the surface, as in the wrist, it can be easily seen or felt. The pulse is strongest in the aorta and gets correspondingly weaker as the blood moves into the smaller peripheral arteries. In the capillaries and veins no pulse can be detected. (Fig. 73.)

Arteries may be roughly separated into three groups on the basis of their size, as large, medium, and small. Each of these groups will reveal certain structural characteristics when examined microscopically, but they will all show a basic three-layered arrangement of the

tissues in the arterial wall. Always forming the lining of the arteries, as well as every type of blood vessel, is the thin endothelium, which is a specialized type of mesodermal epithelium characteristic of the vascular system. The endothelium is separated by elastic tissue elements from the much thicker middle layer, which is composed of smooth muscle fibers intermingled with elastic tissue elements. The muscle tissue of the middle layer is markedly decreased in the large vessels like the aorta and replaced by additional elastic tissue to permit more expansion when large amounts of blood are received from the heart. The third and outermost layer of the arterial wall consists largely of connective tissue, both fibrous and elastic elements being present. The size, strength, and elasticity of the arteries decrease as the distance from the heart increases. Accordingly, the two main arteries are the pulmonary artery, which carries all the blood from the right ventricle of the heart to the lungs, and the aorta, which carries all the blood from the left ventricle and distributes it by connecting arteries to every part of the body except the lungs. The aorta, in particular, should be regarded as the "No. 1" blood vessel of the body, since its walls are the strongest and most elastic in order to handle the blood pumped from the powerful left ventricle.

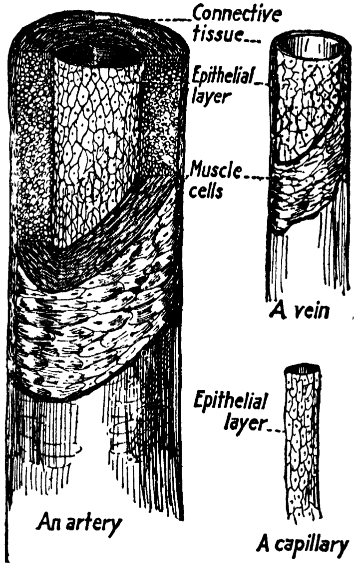
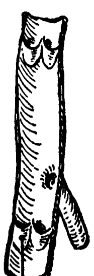


FIG. 73.—The structure of the walls of an artery, vein, and capillary. Diagrammatic. (*Hunter, Walter, and Hunter, "Biology," American Book Company.*)

Veins.—Comparing arteries with veins of comparable size will show that the latter, though built on the same three-layered plan, are not so strongly built as arteries and have relatively less muscle and elastic tissue but more fibrous connective tissue. Another noteworthy difference is found in the valves, formed as tiny flaps in the walls of the veins, which prevent the backflow of blood. The lighter construction of the veins appears reasonable from two standpoints. In the first place, the veins receive the blood at low pressure in a regular slow-



VALVES IN VEIN
FIG. 74.—Internal structure of the vein to show the valves.

flowing stream after it has passed through the capillary network. Consequently the venous walls do not need to be so heavy or so elastic as the arteries so long as they are large enough to accommodate the incoming blood. Also, the veins do not need the well-developed muscle layer because they have nothing to do with the regulation of the amount of blood flowing to a particular organ or region of the body. This is controlled by elements of the nervous system working through the muscle tissue of the arterial walls. As the veins approach the heart, they increase in size and strength, just as do the arteries, in accordance with the amount of blood to be carried. (Figs. 73, 74.)

The chief veins of the body include the superior vena cava, through which the blood from the head region is returned to the heart, and the inferior vena cava, which performs the same function for the blood returning from all the other regions of the body except the lungs. The pulmonary veins return the aerated blood from the lungs to the left auricle. Another very important vessel is the portal vein through which all the blood from the alimentary tract is carried to the liver. This blood, after passing through the liver, is received by the hepatic vein for transfer to the inferior vena cava noted above. (Figs. 75, 81.)

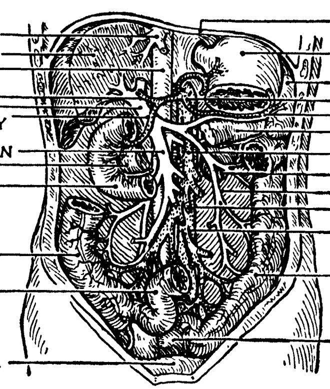


FIG. 75.—Drawing to show the main blood vessels of the abdominal viscera. Note particularly the portal vein which carries the blood from the alimentary canal to the liver (*cf.* Fig. 81*A*). Arteries are stippled; veins, light.

Capillaries.—The capillaries are the ultimate microscopic units of the closed vascular system permeating all the tissues of the body. The capillary walls are very thin, and the blood plasma exudes through them, thus coming into actual contact with the cells of the body. The walls consist only of endothelium—one-cell layer in thickness. The endothelial cells are flattened, irregular in shape, and firmly fastened together to form a tiny tube. They are too small to be visible to the naked eye; some 1,500 of the larger capillaries could be

placed side by side in a space 1 in. wide, and almost double this number of the smallest ones. The latter are so narrow in diameter that the erythrocytes press against the wall as they are slowly moved along, in single file, by the blood current. As a matter of fact, the terminal portions of the arteries and veins, which connect with the capillaries, are not much larger or more complex in their structure than the capillaries themselves. In general, every type of blood vessel, no matter how small, has some muscular and connective tissue elements, the latter definitely separating them from the surrounding tissue cells. Exceptions to this generalization are found in the open channels of the sinusoids, as previously described in the liver, and also in the lymphatic capillaries which may be considered next. (Fig. 73.)

Lymphatic Vessels.—Supplementary to the closed vascular system, with its highly developed arteries, veins, and capillaries and comparatively rapidly circulating fluid medium, is the lymphatic system with lymph vessels, lymph capillaries, and tissue spaces permeating the tissues and often paralleling the blood capillaries. The circulating fluid, lymph, though somewhat variable in composition, may be regarded as being essentially the same as blood plasma containing leucocytes but no red cells. In fact, lymph has its origin primarily in the liquid blood plasma which exudes through the capillary walls, and it is later collected from all the tissues and returned to the blood stream, chiefly through the thin-walled, but comparatively large, thoracic duct which opens into the venous system, anterior to the heart. There is no definite propelling mechanism in the lymphatic system comparable to the heart, and the flow of lymph from the tissues is irregular, slow, and dependent to a large extent upon the muscular activity of the body as a whole. The finest lymph vessels are comparable to the capillaries in size, but the diameter of the lumen is not constant, and the lymph capillaries may end blindly in the tissues, as seen in the lacteals of the villi in the small intestine. (Figs. 81, 83; page 166.)

Course of the Circulation in the Body

We shall now assemble the various parts of the vascular system into a connected system and trace the main routes of the blood in making a complete circuit from the left auricle of the heart through the tissues and back to the same chamber. The complete separation of the right and left sides of the heart establishes two primary routes: the pulmonary circulation and the systemic circulation. In the pulmonary circulation, no variation occurs in the route. The venous blood received from all over the body through the superior and inferior

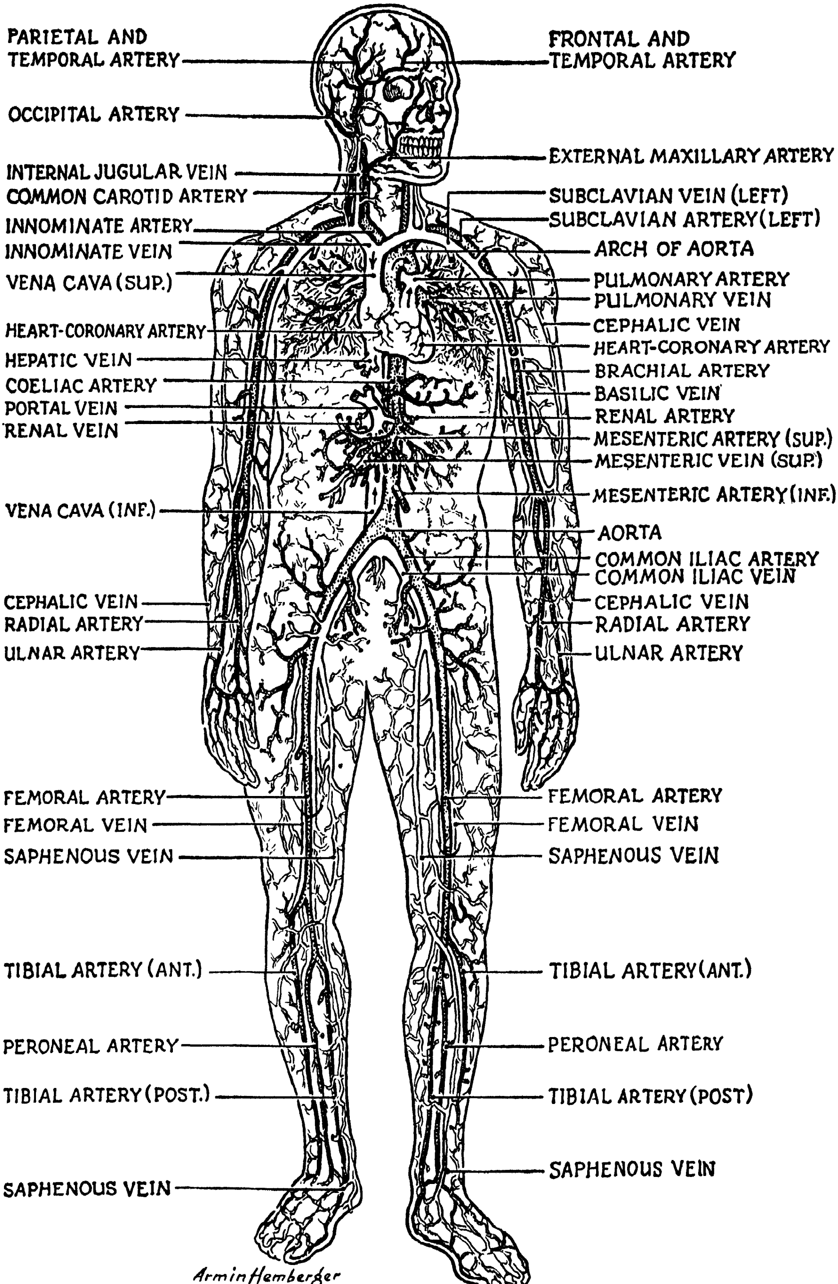


PLATE IX.—Drawing illustrating routes of blood through the chief arteries and veins as described on pages 147 to 152. Arteries are stippled; veins, light.

venae cavae passes into the right auricle, then through the tricuspid valve into the right ventricle. Leaving the latter, it is conveyed through the pulmonary artery to the lungs where it passes through the capillaries, increasing the oxygen content and releasing the carbon dioxide as it does so. Leaving the lungs, the blood returns to the left auricle through the pulmonary veins, thus completing the pulmonary circulation. (Plate IX.)

The systemic circulation is concerned with the circulation throughout the body of the oxygenated blood received in the left auricle from the lungs. The first stage in the journey is the rapid transfer to the left ventricle through the mitral valve and then the departure of the arterial blood from the heart by way of the single large aorta, under the pressure of the ventricular systole. At the conclusion of each systole, as the left ventricle begins to relax, there is a strong tendency for the blood, under pressure in the aorta, to flow back into the ventricle. This backflow is prevented by the quick action of the semilunar valves present in the lining of the aorta, close to its origin in the left ventricle. The semilunar valves are seen as soft, crescent-shaped bags projecting from the lining of the aorta. As the blood starts to flow toward the ventricle, each of the valves instantly fills to capacity and bulges into the lumen of the aorta where contact is made with the other valves in the same condition, thus completely closing the aorta.

All blood leaving the left ventricle passes through the aorta; but since the latter supplies all the systemic arteries of the body, many arteries branch off from it. Immediately after leaving the heart, the aorta curves dorsally and to the left to form the ∩-shaped aortic arch. Referring again to the previous analogy between the right hand and the heart, the second finger, curved loosely toward the palm, will give a general idea as to the shape of the aortic arch. Three important arteries, carrying blood anteriorly, branch from the aortic arch. These are the innominate, left common carotid, and left subclavian. A comparable position on the finger would be just proximal to the first joint for the innominate and distal to the second joint for the other two arteries. Shortly, the innominate divides to form the right subclavian artery and the right common carotid. Thus are formed a pair of subclavians running to arm and shoulder and a pair of carotids, which carry arterial blood to the head.

Just beyond the aortic arch, the aorta reaches the dorsal body wall and continues posteriorly, in a median line, as the dorsal aorta until it nears the posterior end of the abdominal cavity. Here it divides to form a pair of iliac arteries which by means of numerous branches supply the leg tissues. Between the aortic arch at the heart and the

iliac division in the abdomen, various important arteries leave the aorta to supply the alimentary canal, the mesenteries, the liver, and the kidneys. The arterial supply to the liver through the hepatic artery is comparatively small, since most of the blood supply to the liver comes from the various regions of the alimentary canal by way of the portal vein. (Fig. 75.)

It is clear from the description just given that several systemic routes are open to the blood leaving the heart by the aorta. Thus blood may be diverted from the aorta almost at once and proceed anteriorly through the arteries that supply the tissues of the head or those of the arms and shoulder. Or it may continue posteriorly in the aorta and be diverted into an artery supplying the alimentary canal from which it will continue through the portal vein to the liver.

FIG. 76.—Opening of the coronary arteries in the aorta.

Again, the blood may go to the liver directly through the hepatic artery or to the kidneys via the renal arteries or, finally, to any portion of the legs. No matter what route is taken, the circulating blood finally reaches the right auricle through the superior vena cava if it flowed anteriorly and through the inferior vena cava if it went posteriorly. (Plate IX.)

It has been emphasized that the only way for blood to get from the right side of the four-chambered heart to the left is to traverse either the pulmonary or the systemic routes. There is one exception to this statement, and that is found in the route open to the blood which supplies the tissues of the heart itself. It is obvious that the continuously active cardiac tissues must be well supplied with vascular tissues to carry nutritive materials and to remove the cellular wastes. The arterial supply of the heart comes from a pair of coronary arteries which branch off from the aorta just distal to the semilunar valves and form an intricate network of capillaries in the muscle and valvular tissues. The venous blood is collected from the capillary network of the heart by various veins which open directly into the right auricle without passing into the vena cava. Any arterial obstruction that

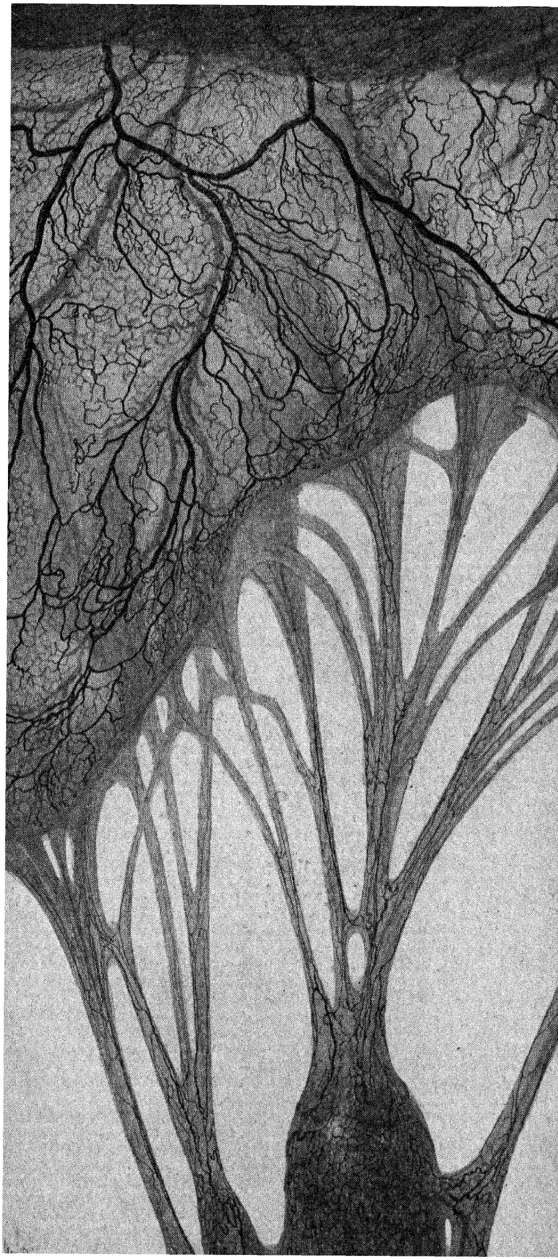


Fig. 77.—Illustrating the high vascularization in the human heart valves. Semi-diagrammatic from injected specimens. (*Courtesy of Dean S. Bayne-Jones. Reproduced from original drawing by Max Broedel.*)

blocks the blood supply to the heart through the coronary arteries is a very serious matter and accompanied by extraordinary pain. This condition is known as *angina pectoris.* If a large heart vessel is blocked, the heart will soon cease to function. If the block occurs in a small artery, partial heart function may continue, but the heart will be permanently impaired by the degeneration of the muscle fibers in the area normally supplied by the blocked vessels. (Figs. 76, 77.)

FUNCTIONAL FEATURES ASSOCIATED WITH THE VASCULAR SYSTEM

With the important structural units of the vascular system in mind, it is next in order to consider the important questions associated with the circulation of the blood through them. In so doing, the functioning of the heart, as the dynamic center of the entire system, supplies a logical beginning for the discussion.

Heart Function

Blood flows through the connected tubular network of the vascular system because it is under pressure. Blood pressure is the result of a rhythmic pumping action of the heart which involves an effective coordination of the muscular walls and the valves of the various chambers. The complete cycle of heart action during which blood is received and then forced out under pressure is known as the *cardiac cycle* or, commonly, as the *heartbeat.* The human heart, under normal conditions, beats from 72 to 75 times per minute, which, if the latter figure is taken, means that the complete cardiac cycle occupies less than 0.8 second. In this tiny unit of time, a regular exact sequence of events must occur, involving a period of relaxation, during which blood is admitted to a particular chamber; a period of contraction, during which the blood is forced into the arterial vessels; and, finally, a rest period, which permits the active muscle fibers to recuperate.

Cardiac Cycle.—Consideration of the cardiac cycle may begin with the contraction (systole) of the right and left auricles. This occurs almost simultaneously in the two chambers and forces the blood into the corresponding ventricles. Auricular systole takes about 0.1 second and is immediately followed by the ventricular systole which drives the blood from the right ventricle to the lungs and from the left ventricle to the systemic circulation. Ventricular systole occupies about 0.3 second. This leaves 0.4 second, or half of each complete cardiac cycle, for a relaxation (diastole) and rest period (diastasis) of the cardiac tissue. No other type of muscle tissue has the ability to carry on the continuous activities of the heart with so little time for recuperation between contractions. When one considers the com-

plicated chemical reactions necessary for nourishment and for supplying energy for muscle contraction, the more difficult it is to understand the basic features of heart function. This difficulty is still further increased where even greater rhythmic activity is maintained, as in the heart of the hummingbird which is stated to maintain a rate of 2,000 beats per minute. (Fig. 78.)

The movements of the heart tissues and valves produce characteristic sounds during systole which can readily be detected by the stethoscope. This instrument was invented over a century ago and enables the trained ear of the physician to recognize abnormal heart action. The first heart sound is given off at the beginning of the ventricular systole and has its origin partly in the closure of the valves between auricles and ventricles and partly in the contraction of the

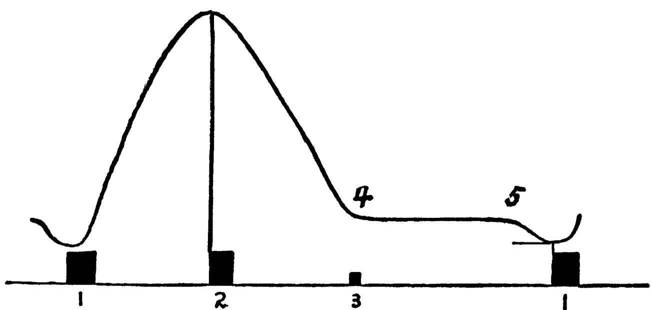


FIG. 78.—Diagram of the cardiac cycle in a dog's heart, as described on page 152. First depression in curve at 1 indicates auricular systole; upstroke, terminating at 2 indicates emptying of heart during ventricular systole; downstroke, terminating at 4, indicates filling of heart during first part of diastole; 4–5, rest period (diastasis). (*Howell, "Physiology," W. B. Saunders Company. After Hirschfelder.*)

ventricular tissues. The sound is best described as a prolonged, low-pitched "lubb." The termination of the ventricular systole is indicated by a short, high-pitched, almost metallic "dup" which is clearly due to the closure of the semilunar valves in the aorta at the end of the ventricular systole.

The origin and the control of the heart beat have been subjects of wonder and experiment from very early times in an endeavor to isolate the essential functional features, which, to the ancients, were a question of vital spirits. Much has been learned about the structure of the controlling mechanism of the heart but very little as to the whys and wherefores, though certain facts stand out. Thus it can be shown experimentally by culturing embryonic heart tissue or by operating on a frog embryo at a very early stage in development that rhythmic contraction of heart muscle begins independently of impulses from nerve tissue. And by cutting the nerves running to the heart in a

mature experimental animal, it is possible to demonstrate that the heart will continue to beat, though the rate may be altered by nerve impulses. Even more, the heart of a frog and various other animals may be entirely removed from the body; but if they are kept under the proper conditions and supplied with fluids of the right chemical composition, rhythmic contraction will continue until the cardiac tissue is weakened by lack of nutrition and accumulated wastes. It is clearly demonstrated, then, that the heart muscle has an inherent rhythmicity. Increased knowledge of heart function, based on many years of experimentation, has not lessened the admiration that has from time immemorial been centered in this most extraordinary organ of life.

Neuromuscular Apparatus.—Careful histological work on the vertebrate heart has revealed the presence of a complicated neuromuscular apparatus which is responsible for the formation and the conduction of the rhythmic impulses that incite the contraction of the cardiac tissues. It has long been observed that the wave of contraction in the heart muscle begins in the right auricle and rapidly spreads to the other regions of the heart. A tiny bit of special tissue, the sinoauricular node (S.A. node), embedded in the wall of the right auricle between the openings of the venae cavae, is the dynamic center of heart action. In some unknown way, rhythmic stimuli, capable of inciting cardiac contraction, develop in it and spread rapidly through the auricular tissue, causing them to contract. Each stimulus is accompanied by an electric action current of sufficient force to be detected by electrical instruments. The stimuli reach the base of the auricles, and here, in the dividing wall, or septum, between the right and left auricles, they stimulate another unit of the neuromuscular apparatus, the tiny auriculoventricular node (A.V. node), from which a bundle of fibers, the auriculo-ventricular bundle (A.V. bundle) continues into the muscular wall between the two ventricles. The auriculo-ventricular bundle soon divides into a right and a left branch, and these subdivide to form a fibrous network throughout the walls of

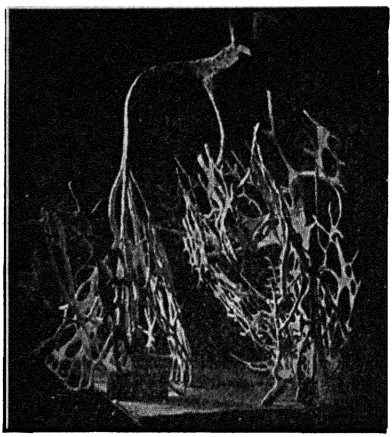


FIG. 79.—Photograph of a model of the neuromuscular apparatus which is embedded in the tissues of the heart, as described on page 154. (*Crandall, "Human Physiology," W. B. Saunders Company.*)

the two ventricles. The auriculo-ventricular node and associated auriculo-ventricular bundle carry the impulses to the ventricles. If the auriculo-ventricular bundle is cut in an experimental animal before it reaches the ventricles, the latter do not contract rhythmically. Other experiments involving disturbances of the normal neuromuscular apparatus show beyond doubt that the secret of coordinated rhythmic heart action is closely associated with this mechanism. The general regulation of the heart beat is a function of the central nervous system, but consideration of this fact may be deferred for later consideration. (Fig. 79.)

Blood Pressure.—The heart moves a lot of blood against pressure. As a result, it does a great deal of work each day. And it never finds it necessary to take any vacation from the routine of the cardiac cycle during a lifetime of high endeavor. It is difficult to ascertain the exact amount of blood forced from the human heart at each systole, but it is in the neighborhood of 4 oz. Beating at the rate of seventy times per minute, this would mean that the amazing total of 27,000 lb. of blood is forced out of the heart every day under normal conditions. This amount is automatically stepped up when the conditions require to possibly ten times the normal output. Thus, it is estimated that the heart of an athlete during the rowing of a strenuous race may pump out 15 gal. of blood per minute, which is more than six times the normal delivery.

But the blood is not merely pumped out of the heart into an open vessel. It is pumped into closed vessels against considerable pressure. The difference is that existing between a common well pump delivering water into an open bucket and a fire engine pumping water at high pressure into the fire hose. The pressure of the blood in the aorta of man is sufficient to force the blood almost to the top of a vertical tube 7 ft. high. In pumping the blood against this pressure, the heart is doing work equivalent to carrying a weight of 1,100 lb. up 7 ft. every hour of the day and night throughout life and the accomplishment of 189,000 foot-pounds of work per day. Add to this the fact that in active individuals the output of blood from the heart is greatly increased from time to time, as activity increases, and it is apparent that the usual statement of 300,000 foot-pounds of work per day by the heart is not too high.

It is obvious that the blood pressure must be constantly maintained at a sufficiently high level in the arteries to force the blood uniformly to all the outlying regions of the body, without respect to their position. It is possible to determine this level of blood pressure in experimental animals by inserting, into one of the large arteries, a glass

cannula connected by rubber tubing to a manometer. The latter is a U-shaped glass tube partially filled with mercury and designed to show the blood pressure by the amount of displacement of the mercury. It is more convenient to use a U-shaped tube for a manometer than a straight vertical tube, and it is also better to use mercury in the tube rather than water, because mercury is much heavier. The blood pressure, therefore, cannot lift it so high, and the U-shaped manometer tube can be much shorter. When the proper connections are made, the arterial blood will quickly flow through the cannula and tubing and then against the mercury column in the connected arm of the U. The level of the mercury in this arm of the manometer will be depressed and correspondingly elevated in the other arm in accordance with the amount of blood pressure. The pressure can be recorded in linear fashion as so many millimeters of mercury (mm. Hg.) by the increased length of the mercury column in the unconnected arm of the manometer. (Fig. 80.)

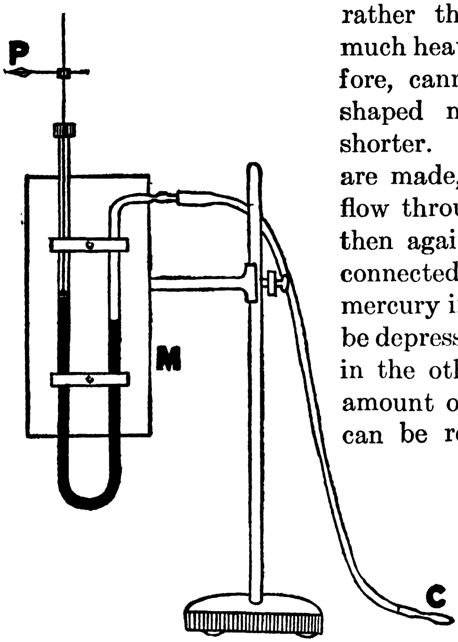


FIG. 80.—Blood pressure manometer as described on page 156. *C*, cannula for insertion in the artery; *M*, U-shaped tube with mercury; *P*, writing point for tracing the record. (*Mitchell.*)

It was early recognized that blood pressure was an important factor in the diagnosis of human disease, and consequently it was necessary to devise a convenient and easy method of obtaining it that did not involve opening an artery. This was accomplished about fifty years ago when the sphygmomanometer was devised. The principle of this instrument is the same as that of the manometer, but, instead of inserting a cannula in a blood vessel, an inflatable band of rubberized cloth is wrapped around the patient's arm, just above the elbow. When this band is inflated by pumping air into it, pressure is applied to the arm; and when this external pressure equals that of the blood in the artery, the flow of the blood is stopped at the pressure area. The cessation of flow can be determined by the absence of the pulse in the brachial vessel below the inflated band. The use of the stethoscope just below the band will give the critical point with accuracy. In determining blood pressure by this method, the air pressure around

the arm is increased until the sounds in the vessel have entirely stopped. Then the air pressure is released gradually until the first sounds of the returning pulse are heard. The air pressure at this point, read as millimeters of mercury from the air gage which is also attached to the pump, is taken as the systolic pressure. Now with this point determined, if the pressure around the arm is gradually reduced still further, a point will be reached where the diastolic sound, which marks the low point of arterial pressure, can be detected. In the young adult, the normal systolic pressure is found to be from 120 to 125 mm. Hg, and the diastolic pressure about 70 mm. Hg. In general, in women of comparable age, the pressure is about 10 mm. Hg less.

The difference of about 50 mm. Hg between systolic and diastolic pressure, as just obtained, gives a definite indication of the elasticity of the arterial walls. This factor of arterial elasticity tends to decrease in the older individuals as the arterial walls become more and more rigid. Accordingly, the ability of the arteries of the older person to compensate by expansion for the increase in the amount of blood at each systole is reduced. Correspondingly the blood pressure throughout the entire arterial system is increased. This is known as *hypertension*. A certain amount of increase in blood pressure is the normal accompaniment of age, but, under certain disease conditions, marked increases occur in which the systolic pressure may rise over 200 mm. Hg. Such conditions are bad for the heart as it has to do extra work in pumping the blood into the arteries against the increased pressure, and the extra pressure may also result in the rupture of an important but thin-walled vessel, as in the brain—the condition of apoplexy.

The blood pressure in the circulatory system is greatest in the aorta near the heart which receives the full force of the blood from the left ventricle at each systole. The pressure in the pulmonary artery is much less, in fact, slightly more than a third of the aorta. In all cases, the blood pressure is reduced as the arteries get farther from the heart and subdivide into smaller and smaller branches in the tissues. In the human capillaries, the pressure is reduced to about 22 mm. Hg; and in the connecting veins leading back to the heart, the pressure continues to decrease until this organ is reached. The flow of the venous blood into the heart is aided by a negative pressure in the thorax which may amount to as much as -8 mm. Hg during an inspiration.

Blood pressure as a whole is dependent, under normal conditions, upon two factors: the amount of blood pumped out by the heart and the peripheral resistance. Both of these are subject to wide variation in the normal activities of an individual. Just as soon as an increase

occurs in muscular activity, the call for increased aeration of blood brings about an increase of heart activity, and more blood will be forced through the vessels which will tend to raise the blood pressure. The peripheral resistance can be altered through nervous and muscular action in the walls of the vessels which results in increasing or decreasing the size of the vessels in a particular organ or region of the body; the blood pressure will be increased or decreased accordingly. Under abnormal conditions, the blood pressure may be affected by other factors. Thus, as noted above, a decrease in the elasticity of the arterial walls increases the blood pressure. Again, when large quantities of blood are lost by bleeding, the blood pressure falls until the liquids are restored. Certain diseases are known that reduce the viscosity of the blood. This also tends to reduce the blood pressure because the thinned blood will flow more easily through the vessels and reduce the peripheral resistance.

Transportation of Materials in the Blood

Nutritive Materials.—The products of digestion that have been absorbed from the digestive tract and transferred to the vascular system are carried in solution in the blood plasma. As already noted, the numerous smaller vessels permeating the walls of the alimentary tract finally unite to form the large portal vein through which all the blood from this region is carried to the liver. The various activities of the liver in the chemical treatment of the carbohydrates and proteins have been previously noted. The transportation of the digested fats is very largely through the lymphatic vessels rather than the portal vein. It will be remembered that each villus in the intestinal wall contains a lymphatic capillary, or lacteal, which ends blindly near the tip of the villus. The best evidence is that the fatty acids and glycerol, resulting from the digestion of the fats, are absorbed in combination with the bile salts by the mucosal cells. The bile salts are split off from the fatty products in the absorptive cells and soon reach the liver through the portal vein where they are reabsorbed. The fatty acids and glycerol are recombined in the cytoplasm of the absorptive cells to form fats, and the latter, for the most part, pass into the lacteals and then the larger lymphatic vessels, finally passing into the general circulation through the thoracic duct. When fats are stained with a fat stain, such as Sudan III, and then fed to experimental animals, it is possible to trace the course of the stained fat into the blood stream by way of the thoracic duct. Once in the blood stream, the fats are carried in the plasma. (Fig. 81.)

Respiratory Gases.—Consideration has already been given to the main features associated with the transportation of oxygen and carbon

dioxide by the blood stream. The transportation arrangement existing between oxygen and hemoglobin is well established, but there are several difficult problems concerned with the return of carbon dioxide from the tissues to the lungs. The general conception has been that the blood plasma is responsible for the transfer of the carbon dioxide. This is true only in part. The gas analyses of blood show that around

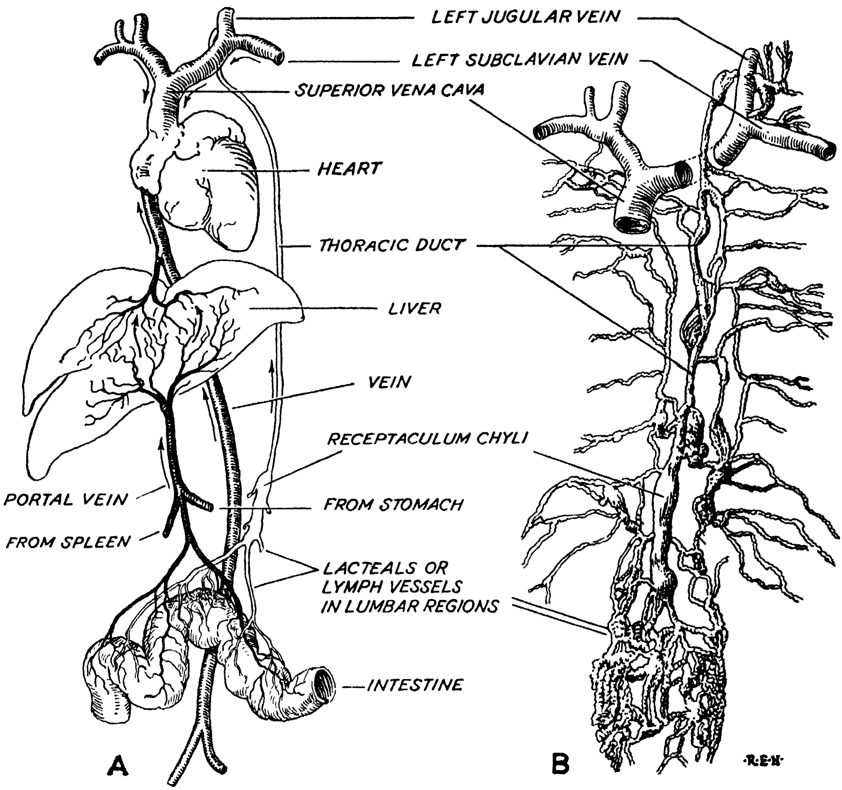


FIG. 81.—*A*, diagram of paths of absorbed food from the digestive tract to the liver, via portal vein; *B*, chief lymphatic vessels in man. *Cf.* Fig. 83. (*Woodruff.*)

55 cc. of carbon dioxide is present in 100 cc. of venous blood. Of this amount, it is believed that not more than 2.5 cc. can be carried in the plasma without chemical change. An additional 20 cc. is carried in the plasma either as carbonic acid (H_2CO_3) or sodium bicarbonate ($NaHCO_3$). The method used for the transportation of the remainder of the carbon dioxide, approximating 60 per cent of the total, presents difficult problems.

It now appears, however, that the principal factor in carbon dioxide transportation is the ability of the hemoglobin in the red cells to vary

its acidity in relation to the amount of oxygen it is carrying. Oxyhemoglobin, formed in the lungs where there is an abundance of oxygen, is more acid than is hemoglobin with the reduced amount of oxygen. In the lungs the newly formed oxyhemoglobin combines with potassium in the red cells to form potassium hemoglobinate, and the amount formed of this compound is directly proportional to the increased acidity of the oxyhemoglobin. When the acidity of the hemoglobin is reduced in the tissues as the oxygen is taken up, some of the potassium is released, and the carbon dioxide received from the tissues enters the blood cells and combines with potassium to form potassium bicarbonate. In the lungs, when the more strongly acid oxyhemoglobin is again formed in the red cells, the potassium bicarbonate breaks down, and the carbon dioxide is released for elimination. Also involved in this picture of carbon dioxide transportation is the so-called chloride shift[1] between the plasma and the red cells (page 91).

The numerous reactions associated with the transportation of one of the main excretions of the cells, carbon dioxide, has just been discussed. The nitrogenous wastes and inorgánic salts liberated by the dismantling of the proteins in the cells are carried in solution in the plasma. The latter are kept at constant levels by the action of the kidney cells. The nitrogenous wastes are first absorbed by the hepatic cells of the liver, converted into urea, and then turned over to the blood plasma once more for transfer to the kidneys. In the collection of nitrogenous wastes, the slow-moving stream of lymph or tissue fluid that bathes the cells is the primary agent.

The internal secretions of the various endocrine glands are poured directly into the blood stream as was seen in the previous chapter. So far as is known, all of the internal secretions are carried in solution in the blood plasma.

Uniformity and Variation in the Blood

The ability to maintain an essentially uniform condition necessary for cellular activity, in spite of the variety of materials poured into it by every cell of the body, is one of the outstanding features of this liquid tissue. Concerned in the maintenance of this uniformity in the blood are several associated organs which have been previously noted but may well be brought together at this point. Thus the respiratory center in the nervous system endeavors to keep the carbon dioxide content of the blood within the prescribed limits by accelerating the rate of breathing when it gets too high and retarding the rate when

[1] Consult Appendix: Chloride Shift.

the opposite condition occurs. The liver looks after the carbohydrate levels in the blood by converting the stored glycogen into glucose and secreting it as needed to maintain a level of approximately 0.1 per cent in the blood, which is available for fuel by the cells. Another important action of the liver, which promotes blood uniformity, is in the maintenance of the normal fluid balance by immediately removing excess fluids absorbed from the digestive tract and later releasing them as needed. In this connection, the action of the kidneys is also important both for the fluid balance and for keeping the salts of the blood at the proper levels.

Buffering.—But in addition to all these cooperating organs the blood plasma is equipped with its own apparatus to insure blood uniformity with respect to the important acid-alkaline equilibrium. This process, known as *buffering*, enables the blood to maintain the normal slightly alkaline condition (pH 7.3 to 7.5)[1] except under serious disease conditions as might result, for example, from continued diabetes. When an acid is added to pure water, which has no buffering power, the neutral condition of the water is changed at once to an acid condition, and the amount of acidity increases in direct ratio to the amount of acid that is added. If an alkali were added to water, the alkalinity would be increased in the same way. In a buffered liquid, such as the blood, the addition of an acid or an alkali does not change the previous acidity or alkalinity of the liquid; that is, the pH remains the same up to a certain point because the buffered liquid contains substances, buffers, which combine with the added acid or alkali and thus neutralize their effect. This action in the blood or other buffered liquids will continue until all the combining substances or buffers are used up, after which the addition of an acid or an alkali will, of course, immediately change the acid-base equilibrium of the liquid.

Blood contains substances that buffer it against both acids and alkalies, but it is more strongly buffered against acids. The buffers in the blood include the proteins in the plasma and, in particular, the hemoglobin in the red cells and various salts. The extent of buffering in the blood against acids depends upon the alkaline reserve, and this is indicated by the ability of the blood to combine with carbon dioxide. This is due to the fact that the latter, in entering the blood, unites with water to form carbonic acid. The amount of carbonic acid that can be neutralized by the blood without changing its normal alkalinity is a true indication of its protection against an acid condition. The normal carbon dioxide combining power of the blood has been found to be around 60 volumes per 100 cc. of blood. Any increase in the acids received by the blood tends towards acidosis, because the alkaline

[1] Consult Appendix: Hydrogen Ion Concentration.

reserve is reduced by their neutralization. Normally this reduction of the alkaline reserve can be compensated for by an increased elimination of carbon dioxide through the lungs, but sometimes, as in the case of severe diabetes, the acids received by the blood are increased to such an extent that the alkaline reserves of the blood are depleted in spite of all that can be done. When this happens, the normal alkalinity of the blood is disturbed to such an extent that it may even become slightly acid with very serious consequences.

Variable Factors.—But the provisions for functional diversity, or variation, in the vascular system as a whole are as impressive as those concerned with uniformity of the blood, for they enable the organism to adapt itself to the changing conditions of the environment—both external and internal. The vascular system is one of the most adaptable units in the entire body. One or two important examples may be cited. Consider first the response of the heart when heavy muscular activity is begun. Almost at once a largely increased amount of blood is pumped to the tissues. Under very severe conditions, it is believed that the heart may increase its output to as much as ten times the normal rate. Associated with this activity is an increased amount of blood but, more particularly, an increased rate of flow through the vessels due to the higher pressure.

Due to the fact that the supply of blood in the body is not sufficient to maintain the metabolic functions in all the organs at a maximum rate of operation simultaneously, adequate supplies of blood must be given to those organs where it will do the most good for the organism as a whole at a particular time. One of the best and most common examples of this fact is in connection with nutrition, for it is found that after a hearty meal blood is collected from all over the body and sent to the vessels that supply the tissues of the alimentary tract. This additional blood enables the secreting cells of the mucosa to be fully supplied with all their requirements while they are working at a maximum rate to furnish digestive enzymes. It also provides for the rapid transportation of the absorbed food to the liver and then to all the cells of the body. The extra blood supply to the nutritive organs at such times is collected from all over the body but possibly more particularly from the skin. This has a tendency to make the person feel chilly; so it is that a warm quiet corner for a time after a meal is particularly enjoyable. Possibly even more striking is the marshaling of the blood away from the skin and into the vital organs and muscles when the emergency hormone adrenine is thrown into the blood as previously described (page 111).

Regulation of many kinds is occurring continuously in the vascular system. The varying conditions of the blood—the amount of carbon

dioxide, the presence of a little excess of certain secretions, muscular activity, and even the position of the body—are all effective in altering the blood flow. Associated in all this regulation is an amazing system of checks and balances, which are, to some extent, integral parts of the vascular system and also, to some extent, elements of the nervous system located in the vascular tissues. The relations existing between the vascular and nervous tissues are complex and intimate, as will be seen in the later chapter devoted to the Nervous System. It may be stated here, however, that the wall of every type of blood vessel, from the smallest capillary to the largest vein or artery, contains a network of nerve tissue through which the conditions in the vascular system are ascertained and regulated. The abundance and complexity of nerve elements in the vascular system undoubtedly reach a climax in the tissues of the heart itself, because the regulation of the heart beat is of basic importance to every cell in the body.

Two other features of the blood stream, which render service in the protection of the organism when certain emergencies arise, are noteworthy. These are the ability of the blood to prevent excessive loss by bleeding, provided the injury is not too serious, and, secondly, its very great power to control infection when a parasitic microorganism secures a foothold in the body tissues.

Blood Coagulation

Every drop of the 6 qt. of blood in the body is rightly regarded as a precious material that must be conserved whenever possible. There was a time not so long ago when physicians did not recognize this fact, and bleeding for various ailments, with consequent wastage of blood, was a common practice. The only thing that saved the patient following such treatments was the amazing ability of the vascular tissues to regenerate the blood plasma and cells. This ability is so marked and the regeneration processes so rapid that a normal individual can lose a considerable amount of blood without experiencing more than a temporary weakness. But the organism endeavors not to lose blood; and as soon as a vessel is injured and bleeding starts, the clotting mechanism in the plasma goes into action, and a series of complex chemical reactions begins which soon results in changing the blood plasma issuing from the wound from a free-flowing liquid to a rather firm jelly-like mass which completely occludes the break in the wall of the blood vessel, unless the latter is too large, with a consequent rapid flow of blood from it. The blood clot continues to increase in strength, and in a comparatively short time is about as firm as the original tissue.

The blood clot represents the culmination of a complicated series of

chemical reactions in the plasma, the complete details of which are not entirely known at the present time. It is widely accepted, however, that a protein substance, cephalin, appearing in the blood only when cell injury occurs (particularly to the blood platelets) acts to neutralize (1) an unidentified blood substance. When this neutralization is accomplished by the cephalin, a chemical union occurs between calcium salts and prothrombin, both in solution in the plasma, to form (2) a new compound, thrombin. When thrombin is synthesized, it reacts with (3) one of the serum proteins, fibrinogen, and this combination results in the formation of (4) fibrin. Fibrin is an insoluble protein material that is precipitated out of the plasma as fine needle-like crystals. These quickly increase in size to form long intertwining filaments in such great numbers that the liquid plasma is soon changed to a gel. Examined under a microscope, the blood clot shows the fibrin filaments present in great abundance throughout. (Fig. 82.)

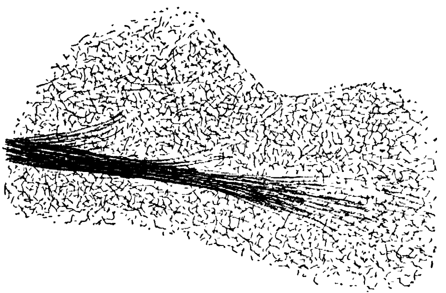


FIG. 82.—Fibrin net as seen when a prepared section of blood clot is examined under high magnification. Note consolidation of fibrin needles to form long fibrils.

Blood drawn from the vessels of an experimental animal and allowed to stand in a container will clot in a few minutes. If the blood is stirred during clotting, the fibrin filaments unite to form long fibers which may be removed together with the enmeshed blood cells as a fibrous mass, leaving behind a noncoaguable blood fluid, or serum. If the blood is left to clot undisturbed, the network of fibrin filaments will undergo spontaneous contraction after a few hours, and the non-coaguable liquid serum will be pressed out of the fibrinous mass. The fibrin filaments form a temporary union of the injured tissues in a wound and are responsible, partially or entirely, for the permanent scar tissue that develops in the site of the wound. After the clot is formed, uninjured connective tissue cells from near-by regions move into the wound area and begin to divide and form new tissue. Leucocytes from the blood stream also congregate in great numbers and prey on invading bacteria, if any have got into the wound, in an endeavor to prevent infection. The leucocytes also clear up cell debris that has accumulated from the injured and destroyed cells. (Fig. 252.)

Various methods are now established by which the normal process of blood coagulation can be accelerated or retarded or even entirely prevented. Some of these methods have been discovered very recently. Thus during the past few months it has been established

that a hitherto unknown factor, designated as *vitamin K*, is required for normal coagulation, as previously stated (page 61). Contrariwise, various laboratory methods for the prevention of clotting have been in use for some years. Basically, these methods have depended upon the introduction into the drawn blood of a substance, such as sodium or potassium oxalate, that would precipitate the calcium in the blood and thus prevent fibrin formation. Also, it has long been observed that the bloodsucking leeches and other similar pests secrete a substance (hirudin) from the salivary glands that prevents coagulation of the host blood at the wound site while the parasite is gorging itself. Of particular importance, however, as an anticoagulant is a substance, heparin, which is now secured in considerable quantities from the liver, lung, and various other tissues of cattle as a result of several years' research. It is believed that heparin will be of great value in medicine in the prevention and treatment of blood clots, particularly in the coronary vessels of the heart.

A well-known hereditary disease, hemophilia, is characterized by a complete or partial failure of the blood to coagulate. This failure is apparently due to a defect in the chemical reactions. Individuals thus afflicted are known as *bleeders*, because even a slight wound may result in a fatal hemorrhage. The basis for the hereditary transmission of this defect is indicated in a later chapter (page 383). It is possible, though not as yet established, that the hereditary deficiency may be associated with a lack of vitamin K rather than with plasma elements.

Control of Infection

The control of infection, which always results from the invasion of a disease-producing organism, is largely a function of the vascular system. This may be accomplished in two ways. In the first place, there are certain chemical substances, known as *antibodies*, which appear in the plasma of the blood following an infection. Their exact nature is unknown, but it is evident that they are able to render the environment of the host unsuitable for the invading organisms. Antibodies are produced, presumably by the cells of the host, and given off into the blood stream. Another method used in the control of infection is through the leucocytes of the blood, which, as noted above, are amoeba-like in structure and phagocytic in their nutrition. At the time of an infection, the numbers of leucocytes are greatly increased, and they congregate at the focus of infection and ingest the invading microorganisms. They are aided in this work by a particular type of antibody, the opsonins. Further consideration of infectious disease is given in Chap. XVII.

Of course, it is the lymph that actually bathes the body cells and therefore comes into immediate contact with the infected areas and the invading organism. The lymph, supplied as it is with leucocytes and antibodies, is a first line of defense against invasion. But the tissue fluids in flowing through an infected area may become contaminated with some of the parasites or with substances harmful to the tissues of the host. Accordingly, lymph returning from the tissues must not be permitted to enter the blood stream for general circulation until it has passed through filtering stations equipped to remove the foreign materials or to render them harmless. This is the function of the lymph nodes which are present at many strategic points along the routes of the lymphatic vessels. A typical lymph node may be described as a small body, comparable to a bean in size and shape, consisting essentially of a special lymphoid tissue. It is encapsulated with connective tissue and connected with afferent and efferent lymph vessels. The lymph slowly filters through channels in the lymphoid tissue, and the cells of the nodes are normally able to render the lymph harmless before passing it on to the blood stream. When the presence of a harmful foreign substance is detected, the activity of the nodes increases; they become enlarged and more or less painful, as in the case of an infected throat or finger. (Fig. 83.)

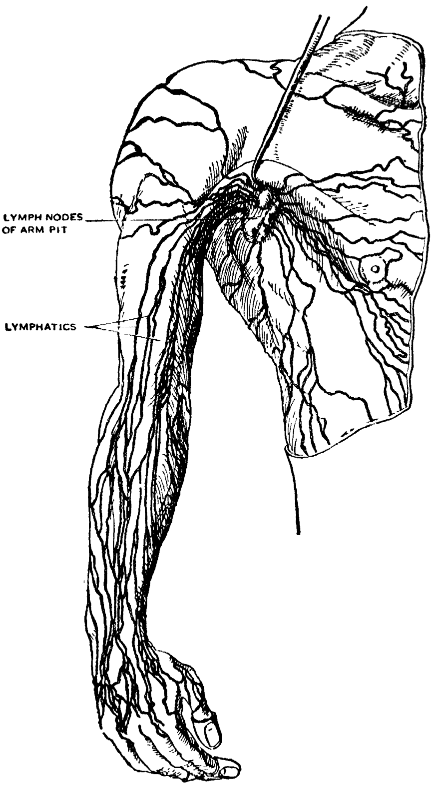


Fig. 83.—Illustrating the lymphatic vessels of arm and chest. These join the thoracic duct (Fig. 81*A*). The chest muscle is drawn away to expose the lymph nodes of the arm pit. (*Haggard, "Science of Health and Disease," Harper & Brothers.*)

The Spleen

The spleen is situated in the upper left-hand region of the abdominal cavity, below (dorsal) the cardiac portion of the stomach. It is the largest lymphatic gland in the body and is abundantly supplied

with blood through the splenic artery and drained by the splenic vein. As a lymphatic organ, the spleen is unique in that it is directly connected with the blood vascular system rather than with the lymph channels. Histologists have shown that the lymphoid tissue of the spleen may be differentiated into a so-called white pulp, which appears to be primarily associated with arterial vessels, and a red pulp through which the blood passes before reaching the venous connections. No direct connections exist between artery and vein through a closed capillary system. In fact, the exact course of the blood in the splenic tissues is still in doubt. Intermingled throughout the functional splenic tissues are connective tissue elements, together with well-defined blood vessels and possibly muscle elements. (Fig. 75.)

Functionally, the spleen remains the great mystery organ of the body. Suggestions as to its function are numerous and varied. But whatever its services, none of the functions is absolutely essential to the adult organism, for the spleen may be removed from experimental animals without essentially affecting the vital functions. However, certain established facts do indicate important splenic functions in the normal vertebrate organism, all of which are apparently taken over by the other organs if the spleen is removed. In the first place, the spleen is clearly associated with the vascular system in a number of ways, notably in the destruction of senile erythrocytes and the subsequent formation of bilirubin, a function that, according to most authorities, is shared by the cells of the liver and of the bone marrow. The spleen is notably rich in iron compounds, and it must be that the splenic cells save and store the essential iron from the disrupted hemoglobin molecule and make it available for hemoglobin synthesis when needed. There seems to be little question that the spleen serves as a reservoir for reserve stocks of normal erythrocytes to be released as needed following serious hemorrhage or other abnormal demands. Again, it appears clear that the spleen is continually forming leucocytes for the blood stream and that, in the human embryo, during fetal life, it also forms red cells in great quantities. The nature of the reaction in nutrition is not understood but is clearly indicated by the fact that a marked increase in the size of the spleen occurs after each meal, the maximum size being reached some 5 hours later. Finally, considerable data are available that give strong evidence for an important function of the spleen in the defense of the body following various infections, particularly of the blood, through the formation of antibodies and phagocytic cells.

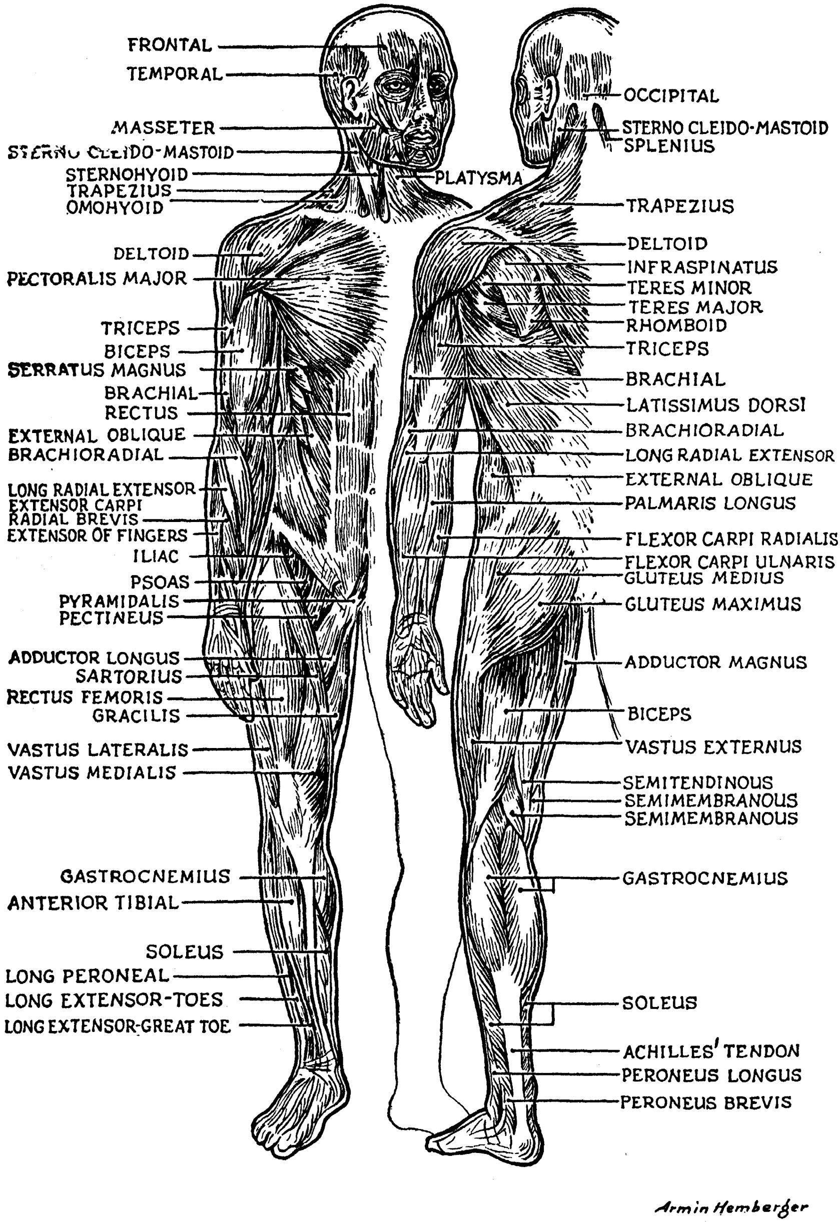


PLATE X.—The chief muscles of the human body as seen from the ventral and dorsal aspects.

CHAPTER VIII

BIOLOGY OF THE MUSCULAR SYSTEM

It should be evident from the study of the various organ systems as given in the previous chapters that there is a widespread demand in the animal body for contractile tissues to perform the many types of movements essential to the various functions. The primary functions of nutrition, respiration, and transportation are all closely bound up with the activities of muscle tissue. But even so it should be remembered that the muscular system, in supplying motor service to the various other organ systems of the body, is by these same acts helping to supply its own needs, for each muscle cell must continually receive essential materials and be relieved of the metabolic wastes, services supplied by the other systems. And so it is with all the tissues and organs in the body; they give to all and receive from all.

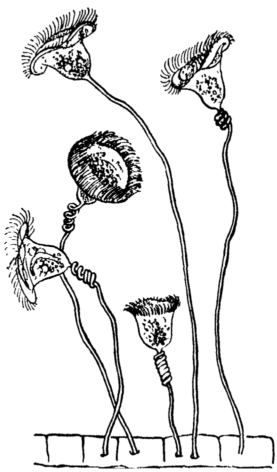


Fig. 84.—Group of unicellular Vorticellae, each attached to the surface of a water plant by a contractile filament containing myoneme fibers. (*Redrawn from Sedgwick and Wilson, "General Biology," Henry Holt & Company, Inc.*)

Muscle tissue, as the essential unit in voluntary bodily motion, has its own particular function in the organism in addition to the general assistance it renders to the other organ systems. This special function of the muscular system, voluntary movement, is continually evident in the motions of the appendages in doing the almost numberless things that fall to their lot, including locomotion, which involves the movement of the entire organism from place to place. Locomotion of some kind is essential for the nutrition of most animal types. Voluntary movement, then, as the distinct function of the muscular system, may well be distinguished from involuntary movement in which special varieties of muscle tissue are built into the functional units of other organ systems to supply the particular type of movement essential to the various functions.

STRUCTURAL FEATURES ASSOCIATED WITH MOVEMENT

Contractile elements are found even in the one-celled organisms. Thus, the familiar bell-shaped protozoan Vorticella supplies a particularly good example of a contractile element in the so-called *myoneme fibers* which originate in the wall of the bell-shaped body and converge to form a contractile filament in the handle, or stalk, of the bell, by which the animal is attached. Any disturbance causes the tiny Vorticella to contract into a spherical body, with the attached filament drawn up like a tightly coiled spiral spring. In the primitive multicellular organisms, such as the Coelenterates, contractile elements are present in many of the cells. Hydra serves again as a good example, for the ectoderm that covers the outer surface and forms a large part of the body wall, consists chiefly of epitheliomuscular cells which show marked power of contraction. Muscle tissue in higher animals is built up by the union of many cellular elements to form definite units which function only in contraction. It develops from the mesoderm and accordingly is found only in the triploblastic animals. It is well shown in the body wall and alimentary canal of the earthworm. And one of the most noteworthy types of muscle tissue, possessing amazing functional ability, is found in the wing muscles of various insects. Another type of wing muscle which is comparable functionally is found in a vertebrate, the hummingbird (page 142). Histological examination of invertebrate and vertebrate muscle tissues show essentially the same structural pattern. (Figs. 84 to 86.)

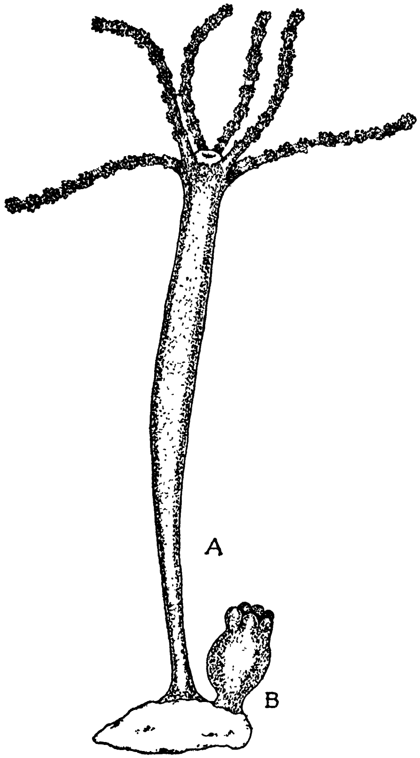


FIG. 85.—External views of the primitive metazoan, Hydra. *A*, expanded; *B*, contracted. (*Haupt*.)

At noted in the earlier chapter on the Organization of the Body, three types of muscle tissue are recognized in the vertebrate organism:

smooth (involuntary), striated (voluntary), and cardiac (striated and involuntary). Our present discussion will deal with muscles as an independent organ system, the *muscular system,* and accordingly is largely concerned with striated or voluntary muscle tissue, which forms many definite motor organs, the separate muscles of the body: each with a particular function, such, for example, as the prominent leg muscles or the biceps muscle of the arm. Before doing this, however,

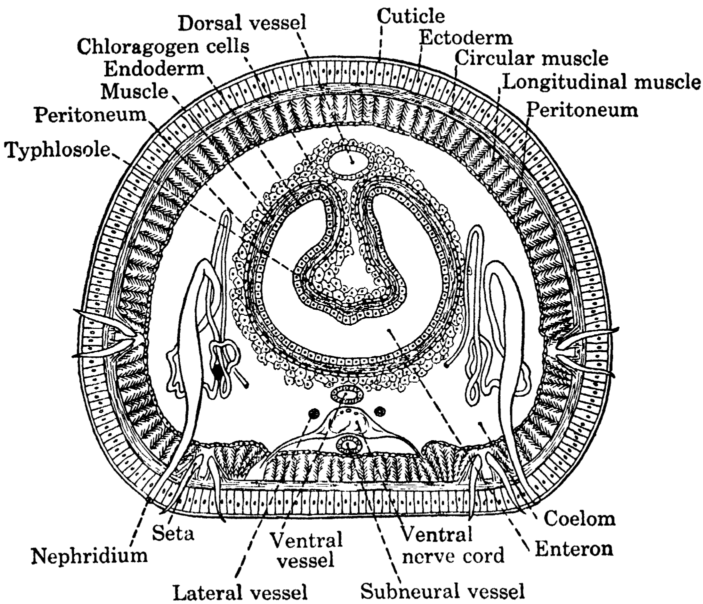


FIG. 86.—Transverse section through the body of an earthworm, illustrating the general arrangement of structures in a triploblastic animal and the presence of muscle tissue in the wall of the alimentary canal and the body wall. Diagrammatic. (*Hegner.*)

it will be well to summarize the main characteristics of smooth muscle tissue.

SMOOTH, OR INVOLUNTARY, MUSCLE

Though unstriated muscle is less advanced in its cellular development than is striated muscle, it rates high in its functional importance. The destruction of even a small amount of smooth muscle tissue in an organ system, such as the nutritive system, will tend to disrupt all the essential functional activities. On the other hand, considerable areas of striated tissue can be destroyed, as in the amputation of one or more limbs, without modifying the vital activities of the organism. Speaking generally, smooth muscle consists of separate sheets of tissue which

are built up by the association of great numbers of independent contractile cells. These muscular sheets act as individual structural and functional units; that is, they are independently innervated, and the constituent cells in a certain area respond as a coordinated unit in producing contraction. When the smooth muscle tissue forms a definite band of contractile tissue surrounding an open cavity, as is usually the case, it will be found that the muscular band is composed of a number of associated sheets of contractile tissue closely aligned to each other. However, many instances occur where smooth muscle tissue does not form definite contractile sheets or bands but instead appears as a localized contractile area containing a few muscle cells and surrounded by connective tissue elements, as, for example, in certain blood vessels. (Figs. 21, 73.)

Throughout the body in whatever location and condition found, smooth muscle tissue is involuntarily controlled through the autonomic nervous system. Smooth muscle tissue does not react so quickly to nerve stimuli as does striated muscle, and it is therefore particularly adapted for the comparatively slow wave of contraction that is characteristic of intestinal peristalsis. It also has great ability to remain contracted or to stay in tone, as the physiologists say, for long periods of time. This characteristic is very important in many of the organs where it is used.

Smooth muscle tissue is widely distributed throughout the body. To get the matter clearly in mind, a number of the more important locations of the unstriated muscle tissue may be listed. In the corium of the skin, smooth muscle forms minute cylindrical units which are connected to the hair follicles so that the hairs stand on end when the muscles contract, and, in addition, it is widely but irregularly scattered throughout the skin. In the alimentary tract, smooth muscle tissue forms definite layers, both longitudinal and transverse. Except for a short distance near the anterior and posterior terminal portions, these layers extend throughout the entire length of the alimentary tract and are responsible, as already noted, for the very considerable motility exhibited in the peristaltic actions. Furthermore, the ducts of the associated nutritive glands as well as those of all the glands in the body contain their quota of smooth muscle tissue. The ducts of the urinary system and the bladder consist almost entirely of unstriated muscle tissue. In a later chapter on Reproduction, the abundance of smooth muscle tissue will be shown in the reproductive system, particularly in the uterus of the mammalian female. Finally, it must be noted that the walls of the various types of blood vessel, with the exception of the heart, which has its own type of

muscle tissue, contain varying quantities of smooth muscle tissue in correspondence with the functional demands.

Striated or Voluntary Muscle

The 374 muscles comprising this organ system in man are all connected with the nervous system in such a way as to be under voluntary control. So far as these muscles are concerned, we can move the jaw, wink an eye, pitch a ball, move about a room, or start on a journey around the world by simply willing to do so. Striated

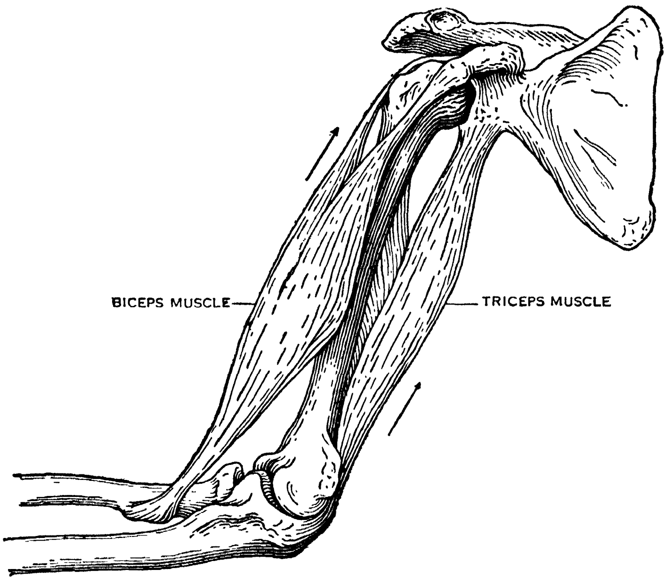


Fig. 87.—Illustrating the pair of opposed muscles (biceps and triceps) which cause movements in the forearm. (*Haggard, "Science of Health and Disease," Harper & Brothers.*)

muscles are sometimes referred to as the *skeletal muscles*, because they are attached to bones and other skeletal elements that form the framework of the body and its appendages. One of the muscle attachments, the origin, is usually fixed and immovable, whereas the other attachment, the insertion, is to a freely movable bone which thus serves as a lever to translate muscle contraction into bodily movement. (Plate X; Fig. 97.)

Muscle tissue exerts power to do work only when it contracts; the relaxation of muscles following contraction has no power to produce bodily movement. This being so, it is evident that to move any part of the body in opposite directions requires two separate muscle units. These must be mounted in such a way that they pull in opposite direc-

tions on the movable bone to which they are attached. Thus the forearm is elevated by the contraction of the large biceps muscle (flexor) lying ventrally above the elbow joint; it is lowered by the contraction of the triceps muscle (extensor) which is also situated above the elbow joint, but on the dorsal side. In the same way there are adductor muscles which draw the limbs backward toward the long axis of the body, and abductor muscles which work opposite to the adductors and draw the limbs anteriorly; or the levators which elevate some part of the body, such as the lower jaw, when they contract; and the depressors which pull in the opposite direction. (Fig. 87.)

Since voluntary muscles are in pairs in order that movement may occur in opposite directions, it follows that one member of the paired muscles must always relax synchronously with the contraction of the other if movement is to be produced in the attached part. If both muscles began to contract at the same time, they would pull against each other, and no movement would result. The synchronous contraction and expansion of the paired, but independent, muscle units involves a nicety of control by the nervous system that is not generally appreciated.

Types of Muscles.—The voluntary muscles that compose the human muscular system may be divided into (1) the segmental muscles which are associated with the head (eye and tongue only), the trunk, and the appendages; and (2) the superficial skin, or integumental, muscles which are almost exclusively located in and around the facial region, just under the skin, and are responsible for a wide variety of facial expressions. If you are pleased as you read this, certain of these integumental muscles are responding to your mental state in a way that a person near by can interpret by noting the expression on your face. The study of muscle development in a vertebrate embryo shows that it is basically segmental. In the lower forms, this definite segmental arrangement of the body muscles is very evident, as can be seen, for example, by removing the skin from a salamander. In adult man and the higher vertebrates, the segmental muscles are plainly evident only in the chest region, under the arms, where they are associated with the ribs. Outside of this region the underlying segmental muscles are covered over by very large appendicular muscles associated with the arms and legs. The appendicular muscles are derived in the embryo from segmental muscles; but in the later development, they lose all evidence of their segmental character. The same origin is true of the integumental muscles in the skin, though it was formerly held that they had an independent, nonsegmental origin in the corium of the skin. (Fig. 88.)

The voluntary muscles show great variation in length and size ranging from the tiny muscles associated with eye movements to the large sartorius of the leg which has its origin in the connective tissues

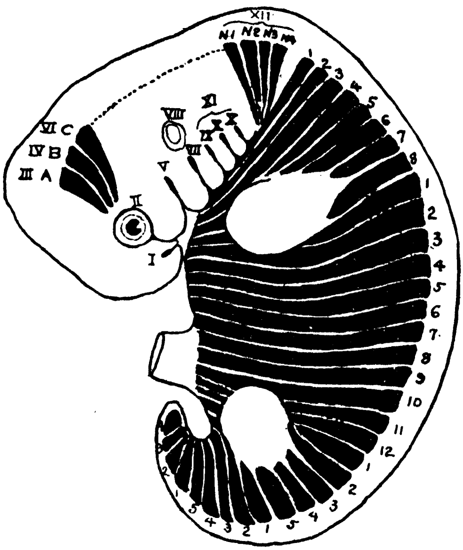


FIG. 88.—Diagram illustrating the segmental arrangement of the muscle rudiments in the human embryo. Roman numerals refer to the cranial nerves (page 242). Segmental myotomes in the various regions of the body are numbered (*A*, *B*, *C*, *N*1, *N*2, *N*3, *N*4, 1, 2, 3, 4 etc.). (*Walter, After Cunningham.*)

of the body wall above the hip joint, and its insertion to the tibia below the knee, thus giving it a length between 2 and 3 ft. In spite of the great variation in the size of muscles, the structural features are essentially the same throughout the body. The larger muscles simply contain a greater number of functional muscle fibers. Each independent voluntary muscle, large or small, is enclosed in a sheath of fibrous connective tissue, the fascia, which is considerably longer than the muscle it encloses. The projecting ends of the sheath, strengthened by additional connective tissue elements, converge to form tendons which are attached to bone or other connective tissue elements at the origin and insertion of the muscle, as noted above. (Fig. 89.)

Motion.—Muscle contraction is translated into bodily motion by the pull exerted on the bone levers through the unstretchable tendons. Tracing the various structures in reverse order, then, we have bone, tendon, fascia, and, finally the muscle which, as the fundamental contractile tissue, gives the original pull. The dissection of a muscle unit shows that it is divided into a varying number of compartments, or fasciculi, each enclosed by an inner layer of connective

tissue, the perimysium, which is, in fact, a continuation of the outer fascia. Within the fasciculi are muscle bundles containing great numbers of microscopic muscle fibers separated from each other by a

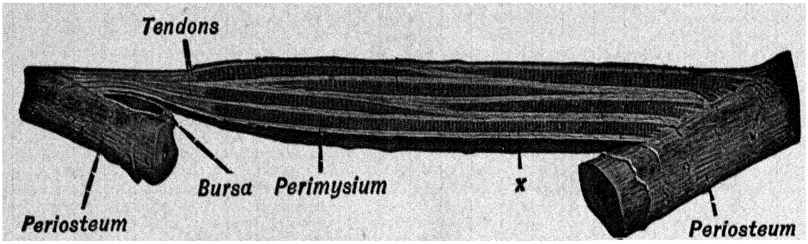


FIG. 89.—Connections between a voluntary muscle, tendons, and bones. *x*, muscle fiber. (*Maximow-Bloom, "Histology," W. B. Saunders Company.*)

still further extension of connective tissue, the endomysium. When the fibers are carefully examined under the microscope, it is found that each one is enclosed in a very delicate connective tissue sheath, the sarcolemma, which represents the final subdivision of the connective tissue elements. (Figs. 89, 90*a*, *b*.)

Histology of Striated Muscle.—It will be well at this point to consider the finer structure of the functional muscle fibers in considerable detail. Each muscle fiber is regarded as essentially a single multinucleate cell, highly variable in size and in the number of nuclei it contains. These thread-like cell fibers usually measure around 0.04 in. in length, but observations have been made in which a length of an inch or more were noted. The diameter of the muscle fiber is usually stated to be about one-tenth of its length, but here again considerable variation has been found. But the individual muscle fibers, with their cellophane-like wrapping of sarcolemma, are not the ultimate microscopic units in the muscle complex, for each fiber consists of great numbers of myofibrils of the same length as the muscle fiber but which, at most, are probably not more than 0.00004 in. in diameter and may even narrow down beyond the limits of microscopic vision. In fact, evidence exists that the myofibrils are repeatedly subdivided to form elongated, ultramicroscopic units finally reaching the molecular level.

The striated muscle fiber is characterized by distinct longitudinal and transverse striations. The longitudinal striations are due to the myofibrils packed closely side by side like thousands of tiny sticks of candy in a glass jar. The glass wall of the jar would correspond to the sarcolemma, or cell wall. The transverse striations are due to the stripings on the individual myofibrils which, instead of going around and around spirally, as in sticks of candy, go directly across each

fibril at right angles to the long axis. Muscle fibers contain another important structural unit, the sarcoplasm, which appears as a transparent, semiliquid substance surrounding the myofibrils and enclosed by the sarcolemma. Sarcoplasm might be compared to a sirup that had been added to the jar filled with sticks of candy so as completely to fill all the interstices between the sticks. To complete the crude analogy, some disc-shaped cinnamon drops, representing the nuclei of the muscle fiber, might be added, which would lie irregularly scattered in the sugar sirup (sarcoplasm) close to the glass wall (sarcolemma). (Fig. 90*c*.)

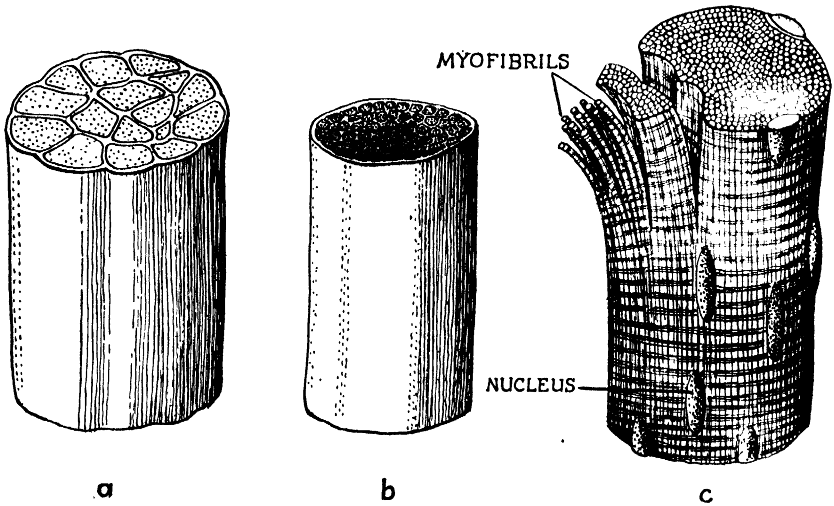


FIG. 90.—Structure of striated muscle. Diagrammatic. *a*, portion of muscle with numerous bundles of fibers (fasciculi); *b*, portion of *a*, showing a single bundle of muscle fibers; *c*, portion of *b*, highly magnified to show a single muscle fiber composed of great numbers of myofibrils (sarcolemma not shown). (*Goldschmidt, "Ascaris," Prentice-Hall, Inc.*)

The fact that each transverse striation continues across the fiber as a regular unbroken line (————) rather than as a series of irregular segments (——_¯¯—¯———_—), corresponding to the markings on individual myofibrils, is due to the fact that the striations on the thousands of myofibrils in a muscle fiber are equispaced and in the same relative position; that is, to refer again to our previous analogy with the candy sticks, the stripes all match when the sticks are lined up beside each other. Careful study of the transverse myofibril striations under the highest powers of the microscope does not answer all the questions about their structural details, but it can be seen that several varieties of transverse markings occur in a regular linear order. In properly

prepared material, alternate light and dark areas (bands or discs) are clearly seen under the microscope.

The dark bands seem to be uniform throughout, but in the center of each light band is a fine granular line (Krause's membrane), which divides it into halves. The light band is commonly designated as the *I*-band; the dark band, as the *Q*-band; and the granular line, as the *K*-band.[1] Without going into further details, it may be said on the basis of studies made with polarized light that the material (molecules) composing the *Q*-band is arranged in definite directions (anisotropic), whereas that of the *I*-band is not oriented (isotropic) and so appears light in color because it reflects light equally in all directions. Beginning with the *K*-band and proceeding along the fiber, the following arrangement of bands occurs; *K*—*I* (light)—*Q* (dark)—*I* (light)—*K*—*I* (light), etc., continuously repeated throughout the entire length of the fiber. Thus the segment of a myofibril from *K* to *K* includes the central dark *Q*-band in contact on each side with the light *I*-band. This linear arrangement of transverse bands is, of course, due to the striation of the constituent myofibrils. On this basis, the fiber is seen to consist of a series of *K* to *K* segments which are termed *sarcomeres*. (Fig. 90*c*.)

The sarcomeres appear to be the basic functional units in voluntary muscle tissue, for close microscopic examination of contracted and relaxed fibers show that these linear units are shorter and wider in a contracted muscle fiber than they are in a relaxed fiber. When muscle tissue contracts, a shortening occurs of the individual fibers with their constituent myofibrils; and this, in turn, is reflected in the contraction of the sarcomeres. Thus it is evident that the sarcoplasm, in which the fibrils are embedded, is not directly concerned with the phenomenon of contraction; it is probably a nutrient material comparable, in a sense, to the blood plasma in its functional relationships to the living myofibrils, the basic functional units of the muscle fiber.

FUNCTIONAL FEATURES ASSOCIATED WITH THE MUSCULAR SYSTEM

Movement in the various parts of our body is so common and universal that there is a great tendency to overlook the various complex phenomena associated with it. Although movement is primarily a function of the muscles; that is, they are the one tissue in the body that is differentiated for the function of contraction, voluntary motion is really a product of three organ systems; the muscular, the supporting, and the nervous. The impulses that incite contraction come from

[1] Terminology used by various authorities for the structural elements of striated muscle fibrillae varies considerably.

the nervous system, and the pull of the muscle, as we have seen, is transmitted through the attached connective tissue tendons to the bones which serve as movable levers and as fixed anchors. Our concern in the present chapter is confined to the phenomenon of muscle contraction. The contributions of the skeletal and nervous systems to bodily movement will be considered in the following chapters.

Muscle-nerve Preparation.—Contractility of muscle tissue will occur independently of any connection with another organ system or even of the body itself. As an example of this, the study of a muscle-

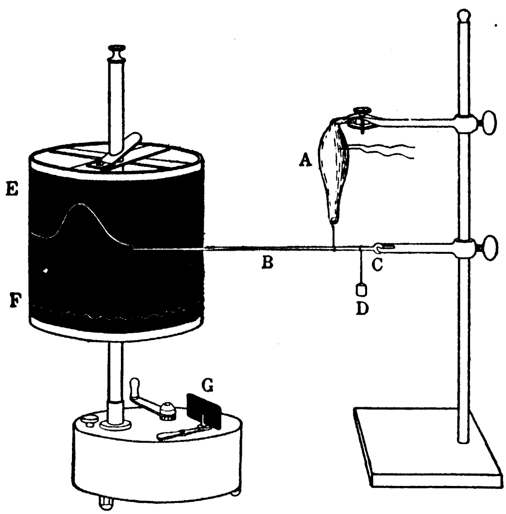


FIG. 91.—Illustrating the method for securing a graphic record of muscle contraction by means of the kymograph, as described on page 180. *A*, muscle, with attached nerve (right); *B*, writing lever with hinge (*C*) and counterweight (*D*); *E*, revolving drum of kymograph with smoked paper attached, on which the record of contraction is made; *F*, time record; *G*, fan for regulating kymograph speed. (*Kimber, Gray, and Stackpole.*)

nerve preparation is of value. Such a preparation is made by carefully removing a muscle, together with the attached nerve that innervates it, from an anesthetized animal. A very good muscle for this work is the large gastrocnemius muscle from the hind leg of a frog. The tendon or bone attached to one end of the muscle is first fastened to an immovable structure, corresponding to the origin of the muscle in the body, and the other end, or insertion, is fastened to a movable lever. The muscle and attached nerve are kept from drying, which would quickly cause the death of these tissues, by the application of an isotonic salt solution. When so treated, an excised frog muscle and nerve can be kept alive and in good shape for experimental work

for some hours. Since no blood supply is available for the excised muscle, it means that the muscle tissues have enough nutritive materials and oxygen stored in reserve to last several hours. Gradually, as these are used up and the wastes also accumulate, the tissues will die. (Fig. 91*A*.)

The muscle may now be directly stimulated by the use of various agents, such as contact, heat, chemicals, and electric current. So long as the muscle remains in good condition, it will respond to these various types of stimulus and contract essentially as it would in the body. Or the muscle may be stimulated indirectly through the attached nerve. When the end of the nerve or any portion of it is subjected to the same irritants, which were used with the muscle directly, a nerve impulse will develop and be transmitted into the muscle in the same way, apparently, as if both nerve and muscle were normally situated in the body and the stimulus for voluntary contraction had originated in the brain. By varying the experimental conditions of the muscle-nerve preparation, a great deal can be learned about muscle and nerve function. Thus the experimenter can determine how long it takes the muscle to respond after the stimulus is given; how long it takes it to relax after contraction; how much work it is capable of doing in lifting a weight at a certain rate per minute; what the conditions are associated with fatigue; the minimum stimulus necessary to cause a muscle to contract; the effect of placing muscle tissue in various gases; etc. It will also be relatively easy, with the proper apparatus, to determine the speed of the impulse passing through the nerve tissue on the way to the muscle and the varying conditions that will incite an impulse.

Study of Muscle Contraction

Two very useful instruments employed by the physiologists in the studies of muscle function are the induction coil and the kymograph. The induction coil is used because, of all the artificial stimuli available, the electric current is best suited, and the induction coil permits the operator easily to control both the strength of the electric stimulus and the exact times at which they are given. The kymograph makes possible a permanent graphic recording of muscle action which can be studied after the experiment. The kymograph consists essentially of a clockwork motor attached so as to revolve a vertical shaft at a uniform rate. A removable metal drum is fastened on the shaft to revolve with it. A strip of smoked kymograph paper of the same width as the side of the drum is wrapped around the drum and attached to it by pasting the ends. When the motor is started, the vertical

shaft, together with the attached drum and covering of smoked kymograph paper, is revolved at a specified number of revolutions per minute which may be varied according to the needs of the experiment. (Figs. 91, 92.)

In recording muscle action, a writing point is fastened to the end of the movable muscle lever of the muscle-nerve preparation and placed in contact with the smoked paper on the drum in such a way that, when the lever moves, a visible line will be scratched through the smoke film on the kymograph paper. If, now, the muscle is stimulated and caused to contract, a line will be scratched on the paper, the height of which will record the amount that the muscle contracted. If, however, the drum is revolving as the muscle contracts, a curve will be drawn on the drum instead of a straight line. Since the drum

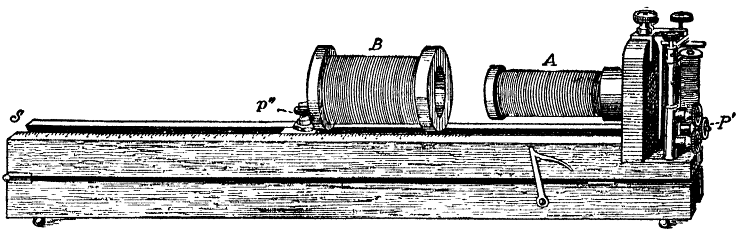


FIG. 92.—Induction coil for muscle stimulus, patterned after the original duBois-Reymond model. Connections with battery are made at P' and p''. Stimulus may be strengthened by decreasing the distance between the secondary coil (B) and the primary coil (A). S, slide with graduated scale. (*Howell, "Textbook of Physiology," W. B. Saunders Company.*)

is moving at a regular measured rate, the length of the ascending curve will indicate the time elapsed during contraction, and the height of the curve from a base line the extent of contraction. As the muscle relaxes, the lever will form a curve sloping down to the base line. The time interval can be graphically recorded on the drum in association with the muscle curve by a separate writing lever attached to a special clock which raises the lever, for example, every hundredth of a second and thus marks the smoked paper. When the complete experimental record is obtained, the smoked paper is carefully removed from the kymograph and dipped into a fixing varnish which quickly dries and thus makes a permanent record. (Fig. 91E, F; 93.)

The data accumulated from this type of experiment show that muscles in different animals and in different regions of the same animal show considerable variation in the rapidity and strength of contraction. Witness the muscle of the insect wing, which requires only 0.003 second to contract in response to a stimulus, whereas the gastrocnemius of the frog requires 0.1 second for the operation. And much slower

still is the involuntary muscle tissue of the vertebrate, which requires several seconds to respond to a stimulus. The elapsed time, between the giving of the stimulus and the beginning of contraction in a muscle, is known as the *latent period.* This, in the gastrocnemius of the frog, is about 0.01 second. Then comes the period of contraction which requires about 0.04 second and, finally, the period of relaxation which is about 0.05 second. The latent period, contraction, and relaxation include the complete cycle of contraction phenomena, and together comprise the *muscle twitch* as distinguished from sustained contraction.

Muscle Fatigue.—When a muscle is given a series of separate electric stimuli, it will respond until it gets tired, or fatigued, provided the stimuli do not come too frequently and so prevent the muscle from

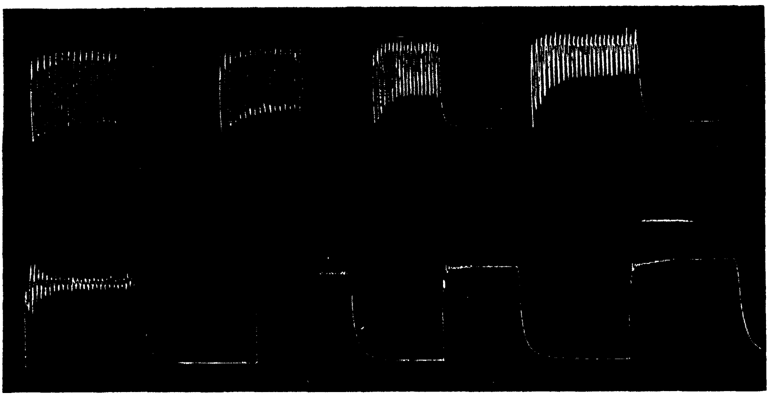


FIG. 93.—Kymograph record showing development of tetanus due to rapid stimuli, as described on page 183. Vertical lines represent single contractions. These disappear as rate of stimuli increases. (*Howell, "Textbook of Physiology," W. B. Saunders Company.*)

completing the relaxation period. Fatigue, which is marked by a loss of irritability, gradually develops, due, apparently, to the accumulation of wastes in the muscle tissue. It occurs in every muscle when subjected to maximum work for considerable periods. In the muscle-nerve preparations, it will be found that the response of the tiring muscle becomes less and less until, finally, it will not respond at all to a stimulus. Normal irritability will be restored after a period of rest. Muscle fatigue under normal conditions in the body is undoubtedly of great value in preventing a complete breakdown and destruction of tissue by over-use.

A fresh muscle will respond to a large number of stimuli, properly spaced so that the muscle has time to relax between shocks. Suppose now that the period between successive stimuli is decreased to such an extent that the muscle does not have sufficient time to relax before receiving another shock. This will quickly result in tetanus, a condi-

tion characterized by a contraction that is maintained until the muscle becomes fatigued. When the period between the stimuli is gradually shortened, the kymograph curves of muscle contraction will show a corresponding decrease in the amount of relaxation with the onset of tetanus, until finally, when stimuli are received at the rate of 20 to 30 per second, the muscle will remain fully contracted, and the kymograph record will exhibit a straight line at the point of maximum contraction. Even so, each stimulus received undoubtedly has its individual effect in keeping the muscle contracted and in preventing relaxation, for, if the time interval between stimuli is lengthened slightly, the individual stimuli are again evident in the record as the muscle relaxes slightly between stimuli. (Fig. 93.)

Ergograph.—For testing and recording fatigue in human muscle tissue, a measuring instrument, the ergograph, has long been used. In

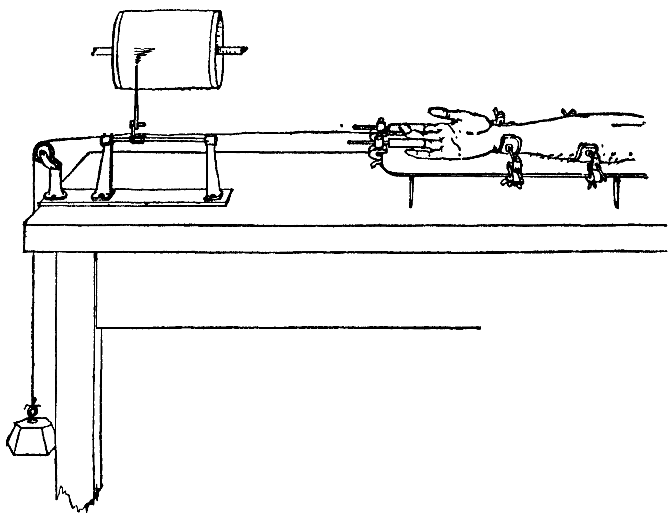
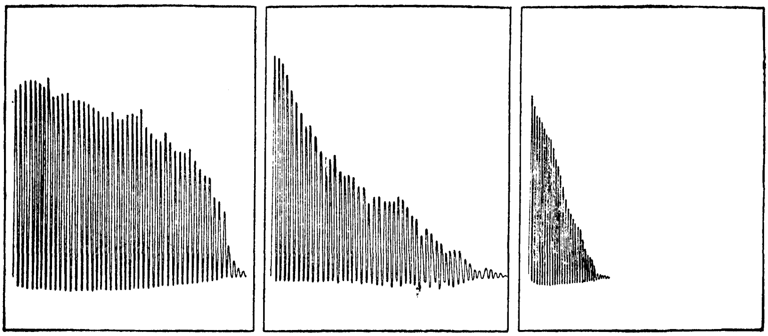


FIG. 94.—Ergograph apparatus used for recording the work done by finger muscles in repeatedly lifting a weight, as described on page 183. (*Haggard, "Science of Health and Disease," Harper & Brothers.*)

using it, the hand is fastened, palm up, on a board placed on a table of convenient height. Then a leather band is fastened around the large middle finger, distal to the second joint so that the finger can be flexed. A string with an attached weight at one end is fastened to the finger band by the other and then run over a pulley fixed at the end of the table. Thus the apparatus is so arranged that, when the finger is flexed toward the palm, the pull is transmitted by the string, and the weight is raised. A writing lever is attached to the string in such a way that each contraction is recorded on the kymograph. By flexing the finger at different rates and also by changing the weight, variation

can be introduced in the experiment. If the weight is raised at short intervals, it will be found that the finger muscles soon become fatigued, and the amount of contraction is correspondingly decreased. If the rapid rate of flexion is continued, a state of complete fatigue is soon reached in which it is impossible for the experimenter to flex the finger at all. From this state of complete fatigue it will require 2 hours for the normal condition of the finger muscles to be completely restored so that the same amount of work can be performed again. With a rest of about 10 seconds between contractions and the use of a proper-sized weight, it will usually be found that the flexure of the finger can be continued indefinitely without fatigue. It is also found that the



A B C

FIG. 95.—Records secured from Ergograph (Fig. 94). *A*, shows gradual development of fatigue in finger muscles when weight is lifted sixty times a minute; *B*, continuation of weight lifting, as in *A*, after a short rest with increasing fatigue. *C*, Rapid fatigue resulting from an increase in the rate to 200 times per minute. (*Haggard, "Science of Health and Disease," Harper & Brothers.*)

muscle activity may vary somewhat in relation to the physical condition of the individual. (Figs. 94, 95.)

Tonus.—An important characteristic of muscle function, which is closely linked with tetanus, is known as *tonus* and may be described as a continuously maintained partial contraction. Tonus is a very important feature of the involuntary muscles of the body, as, for example, in the sphincter valves of the pylorus and urethra, but it is also generally found and prominent in the voluntary muscles. Thus the maintenance of the upright position in man is associated with tonus in certain of the leg and skeletal muscles. Muscle tonus is caused by the nervous system which sends stimuli continually into the muscles concerned. In so doing, the nerve tissue responds to impulses that it receives from various tissues in the peripheral regions. And so in the maintenance of erect posture, proprioceptive impulses (page 271) arising from sensory areas in the muscles and associated tissues of the leg and trunk regions pass into the central nervous sys-

tem and result in efferent impulses which, in turn, maintain the tonus of the muscles concerned.

Muscle Efficiency.—It is possible, with the proper apparatus, to determine the efficiency of muscle tissue as a mechanism, just as the engineer can determine the efficiency of the steam or gasoline engine by calculating the amount of work done with a certain amount of fuel. This is accomplished by using a calorimeter large enough to provide comfortable living quarters for a person during considerable periods (page 86). The calorimeter is also equipped with a machine, known as the *ergometer*, for accurately measuring the amount of work done.

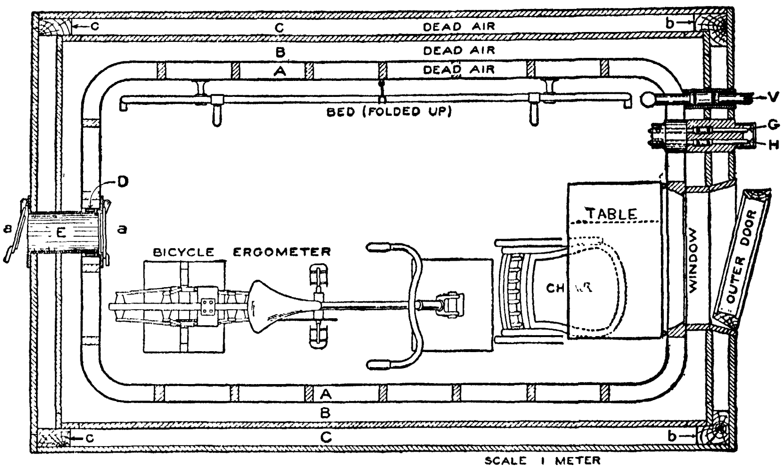


FIG. 96.—Illustrating the Ergometer mounted inside of a calorimeter, as seen from above. *A*, *B*, *C*, *D*, insulation; *E*, food aperture tube; *H*, ingoing water for absorbing heat; *G*, outgoing water; *V*, ventilating air current. (*Howell, "Textbook of Physiology," W. B. Saunders Company. After Atwater and Benedict.*)

The ergometer, designed for this work, is a stationary bicycle with the rear wheel so equipped that the amount of work done in pedaling can be measured and recorded. The calories required per day by the subject of the experiment to maintain the vital activities when he is resting and eating normally are first ascertained over a period of several days. In an important series of experiments, this was found to be 2,397 calories per day. With this amount determined, a measured amount of work was done by pedalling the bicycle-ergometer. Under these conditions it was found that the amount of energy required per day increased to 5,120 calories and that the mechanical work done in pedaling the bicycle proved to be the equivalent of 546 calories. From this series of experiments it is clear that 2,723 calories (5,120 − 2,397 = 2,723) were used in doing 546 calories of work. Dividing the latter figure by the calories used, it is found that the

efficiency of the body as a muscle-machine amounts to slightly over 20 per cent (20.51 per cent) or, in other words, 1 calorie out of every 5 taken into the body is available for work; the other 4 are used in supplying the energy necessary to maintain the essential life functions. Many other experiments, essentially similar in nature, using man and various other experimental animals have given results showing from around 25 per cent (arm muscles) to some 33 per cent (leg muscles) efficiency. The rate of 20 to 25 per cent, as determined for the complete muscular system of man, is somewhat higher than is found in locomotives but less than can be obtained from the operation of modern steam or internal combustion engines under optimum conditions, as in a power plant. (Fig. 96.)

Basis of Contraction.—Inasmuch as it is possible to remove a muscle from the animal body and study the function of contractility under widely varying environmental conditions which can be supplied, it might be thought that the determination of the essential phenomena associated with muscle contraction would be comparatively easy. Exactly the opposite condition obtains, and the great amount of experimental work that has been performed upon the phenomena associated with the contraction of muscle tissue has thus far failed to give definite answers to the major problems involved. The physiologist knows that the energy required for muscle contraction is ultimately supplied by the oxidation of a carbohydrate; he knows that carbon dioxide is released and that a certain amount of heat is evolved. Also the respiratory quotient of about 1.0, which is obtained when the carbohydrate is utilized in the body (page 88), indicates a close relationship between oxidation and muscle activity. Nevertheless, conclusive evidence exists that oxidation is not primarily responsible for contraction, for the latter can occur in the absence of free oxygen. Also it can be shown that the respiratory apparatus of a person running a race requiring a maximum amount of muscular work for a comparatively long period cannot possibly supply enough oxygen to account for the work being done by the muscles. In such circumstances, an oxygen deficit is built up in the active muscle tissues which is gradually paid off later when the muscles are at rest and oxygen, in excess of their requirements, can be supplied. The belief is, therefore, that the energy required for muscle contraction is released by chemical reactions other than those directly associated with oxidation and that the latter process is concerned with building up reserve substances in the muscle tissue that are not directly concerned with muscle contraction.

Chemistry of Muscle Contraction.—Although comparatively little is known with certainty about the chemical changes involved in the

complete cycle of the contraction-restoration-contraction phenomena in muscle tissue, enough evidence is at hand to show that the reactions concerned in muscle chemistry are highly involved. The concensus of opinion at present indicates that the basic reaction in muscle tissue, which releases energy for contraction, is the splitting of an unstable nitrogenous compound, phosphagen, into phosphoric acid and creatine. A relatively small amount of phosphagen is normally present in muscle tissue (around 0.05 per cent). The energy for the resynthesis of the essential phosphagen, following contraction, comes indirectly from the oxidation of glucose in the muscle cells. Apparently the glucose absorbed from the blood stream is converted into glycogen by the muscle cells and stored as a reserve fuel supply. The glycogen can be changed to glucose when needed, and the latter, in turn, changed to lactic acid. The formation of lactic acid from glucose apparently releases the energy necessary for the resynthesis of phosphagen. Here again the process is not direct but through the formation of intermediate compounds. Finally, the oxidation of a certain amount of lactic acid occurs forming carbon dioxide and water, by which sufficient energy is released to maintain the complete cycle of reactions. And, of course, it is known that the hormone insulin is essential to muscle chemistry (page 104).

Just how the energy released by the chemical reactions in muscle fiber is applied to the ultramicroscopic units of the myofibrils so that contraction is induced is entirely unknown, though many theories have been advanced from the earliest times up to the present. The original idea of Galen, held for many centuries, has long since been abandoned; this was that "animal spirits," compounded with air in the brain, flowed into the muscles through the connecting nerves and forcibly distended them. The same fate has overtaken the much later belief, well-established about fifty years ago, that the muscles were essentially heat engines in which chemical energy was converted into heat and that the latter acted directly on the muscle units. Calculations showed that it would require a temperature of about 285°F. in the muscle tissues at the beginning of contraction if they acted as heat engines, which is obviously impossible. It is evident that there must be some arrangement in muscle tissue whereby chemical energy can be directly converted into movement. In other words, heat has nothing to do with contraction; it is a by-product of the chemical reactions. Whatever the methods used to translate chemical energy into muscle contraction, the actual changes in the myofibrils must involve some sort of reversible gelation phenomenon which has its foundation in molecular changes in the individual myofibrils.

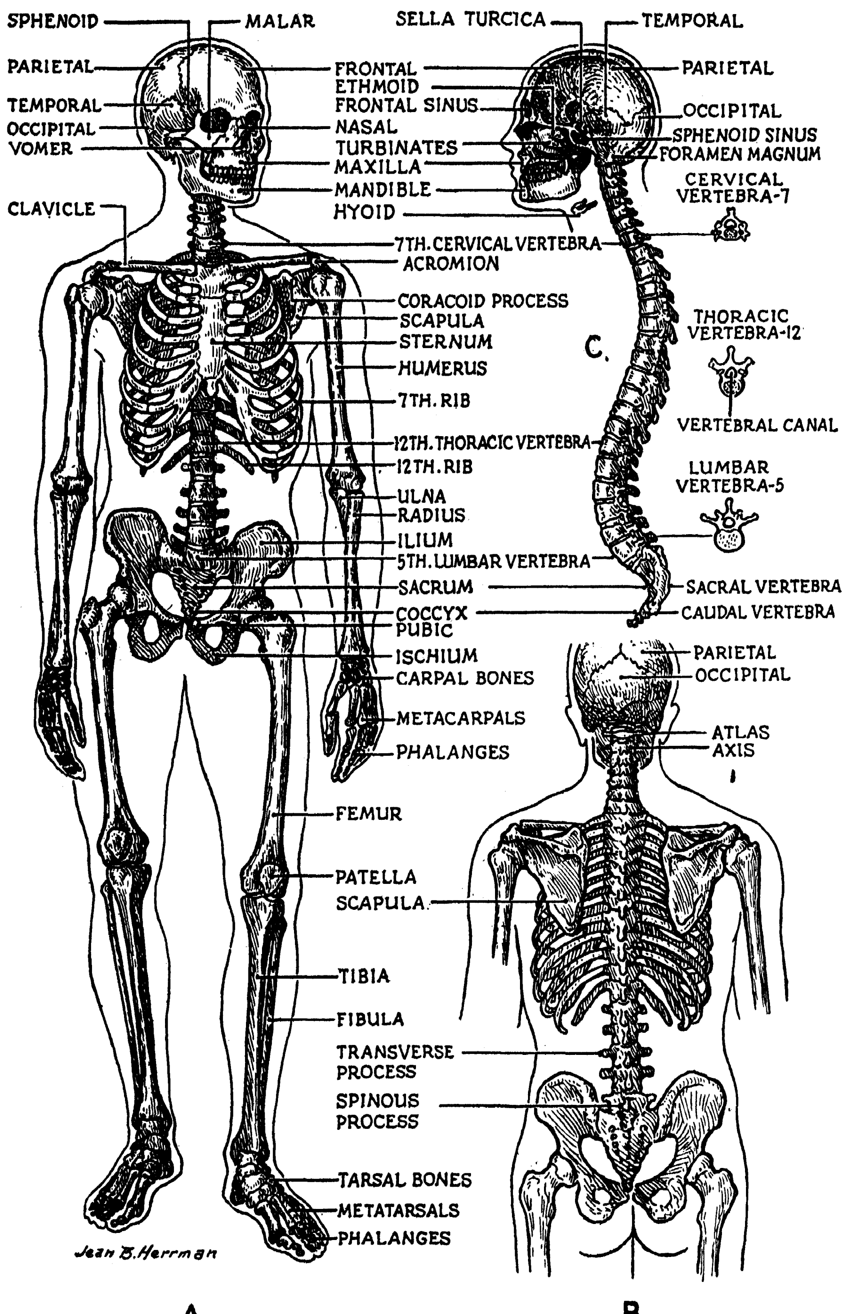


PLATE XI.—The human skeleton. *A*, complete, anterior view; *B*, axial, posterior view; *C*, axial, side view, with the skull sectioned to show internal structures. End views of three vertebrae are also shown.

CHAPTER IX

BIOLOGY OF THE SKELETAL SYSTEM

Another of the five basic tissues of the body, as briefly indicated in the second chapter, is found in the connective, or supporting, tissues. The connective-tissue elements, like those of the vascular and muscular systems, are almost universally distributed through every type of body structure, even down to the individual cells which are held together by an intercellular cement, as is well shown in unstriated muscle tissue. A multicellular organism cannot maintain structural integrity without some sort of cement substance to hold the cells in position, and this material may be regarded as the forerunner of the various specialized types of endoskeletal tissue which develop later. But the connective tissues, unlike the vascular and muscular systems, are relatively inert. They contain comparatively few living cells and much nonliving intercellular material, so that, in general, these tissues need very little assistance from the other tissue systems of the body. Nevertheless, the connective tissues have their independent structural forms and essential functions and comprise, therefore, one of the major organ systems, the *skeletal system*, in the commonwealth of the vertebrate body as well as being heavy contributors to the structural elements of the other organ systems of the body.

STRUCTURAL FEATURES ASSOCIATED WITH THE SKELETAL SYSTEM

As previously indicated, the skeletal system includes various external elements which, together, comprise the exoskeleton and a wide variety of internal connective and supporting tissues grouped as the endoskeleton (page 26).

Exoskeleton

The exoskeleton is probably seen to best advantage among the invertebrate animals, and one thinks at once of the calcareous covering of the island-building corals, the shell of the clam and oyster, or the rigid chitinous material that completely encloses the soft body tissues of the crab, lobster, insect, and their many relatives included in the great arthropod group. The materials used in these outer protecting structures vary greatly, ranging from a comparatively simple inorganic limestone, as in the corals and mollusks, just noted, to much more

complex protein materials, such as chitin in the arthropods and keratin in the epidermal plates of the turtle, and in the hair and nails of the mammals. But this can be said of all the exoskeletal materials; they are nonliving and formed in many instances as noncellular secretions of the underlying living cells. This condition is well shown in the chitinous shell of the crayfish. However, some of the vertebrate animals are not far behind the invertebrates when it comes to exoskeletal structures. The fish covered with scales; the reptiles encased in various types of scaly armor or even by a complete dermal shell, as in the turtle; the feathers of birds; the hairy coat, partial or complete, of the mammals—all these, together with such others as nails, claws, and teeth, are examples of the exoskeletal structures associated with vertebrate animals. (Fig. 97.)

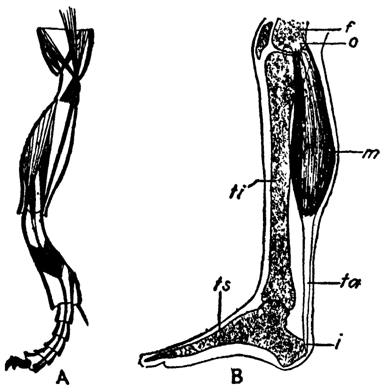


FIG. 97.—Diagrams illustrating the attachment of muscles in leg of insect and man. *A*, insect leg with muscles attached to exoskeleton; *B*, leg of man with muscles attached to bony endoskeleton. *f*, femur; *m*, muscle; *o*, origin of muscle; *i*, insertion of muscle; *ta*, tendon of Achilles; *ti*, tibia. (*Shull. A, after Berlese; B, after Hesse and Doflein.*)

Hair.—Consideration may now be given to the most prominent development of the mammalian exoskeleton, hair, which, as we know, is formed in the tissues of the skin (page 37). Each hair develops in a separate hair follicle consisting of epidermal and connective tissue elements and forming an elongated sac-like structure. The bottom of the hair follicle lies deeply embedded in the dermis of the skin, while the top, with the projecting hair, is at the body surface. Epidermal cells penetrate the dermis, become surrounded by connective tissue elements to form the follicle, and then give off the cells that form the body of the hair. The latter consists of a great number of keratinized epidermal cells which gradually lose their characteristic structural features and become molded as it were, into the body of the hair. They are so closely applied to each other that it is impossible to make out the cellular outlines of the constituent cells, even when a hair is subjected to microscopic examination. A hair is first evident as a tiny projection below the skin surface and continues to elongate indefinitely by the formation of additional cells at the root which is in contact with the hair papilla—a dermal structure at the base of the hair follicle for the nourishment of the hair cells. (Fig. 98.)

The follicles are not permanent structures. They continue to produce the cells that form the hairs for a time and then become inactive, but usually not until cells have been budded off to form new hair follicles in close proximity to the old ones. Sebaceous glands are attached to the hair follicles and secrete an oil which covers the outer surface of the hair. Smooth muscle fibers, present in the dermis, are attached to the hair follicles, and the muscles of each hair are innervated by separate nerve fibers. Thus, hairs do "stand on end" when

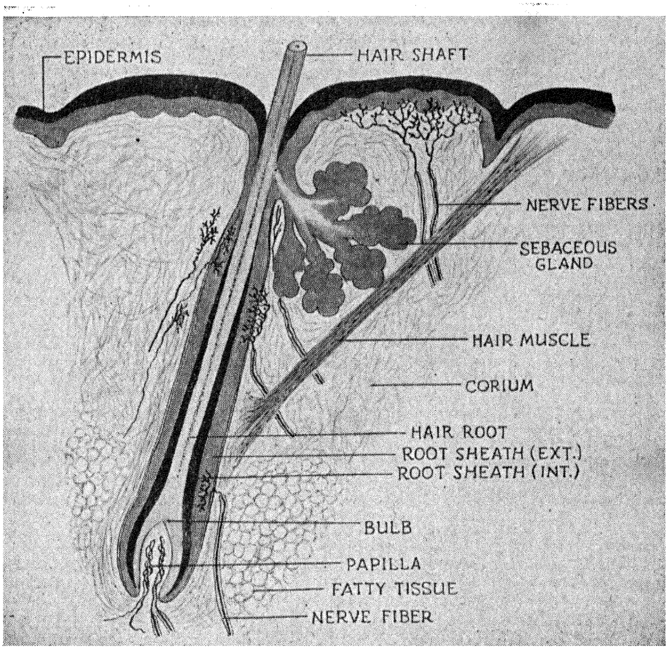


FIG. 98.—Vertical section through human skin showing microscopic structure of hair and hair follicle. (*Maximow-Bloom, "Histology," W. B. Saunders Company.*)

certain conditions cause a contraction of the attached muscles through nerve impulses.

Examined microscopically, a hair is found to consist of two regions. It is covered externally by a layer of very thin cells, irregular in outline, which form a tile-like covering. The main body, or cortical portion, of the hair consists of dense, horny material, the keratin,[1] which has developed through the transformation of the constituent epithelial cells. Keratin is an important protein substance, widely distributed in exoskeletal structures. The amount and color of the pigment present in the keratin of the hair cortex varies greatly, and also air

[1] Consult Appendix: Keratin.

spaces are not uncommon toward the center. Hair color depends upon the amount and quality of the pigment present and its relation to the transparent air spaces. In hairs with a heavier body, such as those of the beard, a definite central area, the medulla, is usually noted throughout the length of the hair. This region is characterized by an irregular cellular arrangement and the presence of large air spaces. (Fig. 98.)

Closely related to the hair in development and structure are the nails of the fingers and toes, as well as the claws of lower types of mammals. Nails are formed from adhering keratinized epithelial cells of essentially the same nature as those which form hairs. The living tissue, which is continually forming and giving off these cells, lies in a fold at the root of each nail and also underneath the nail where it forms the nail bed. The nail is bounded on each side by the nail groove. Receiving additions in length by the additions of cells at the base and in thickness by those added underneath, the nail is gradually pushed forward and projects beyond the nail bed at the tip of each digit. This process, unlike that of the hair follicle, is continuous throughout life, and the nail can grow indefinitely in length if left undisturbed.

Endoskeleton

The bony endoskeletal system is a unique feature of the vertebrates. Invertebrate animals, like the insect, must attach their developed muscles to the inner surfaces of the nonliving exoskeleton and detach them periodically when the shell is shed during moulting. The permanent endoskeleton of the vertebrate serves largely as an inner supporting material, and the soft tissues can thus develop on the outside of the endoskeleton. It may also develop outside the soft tissues and serve for protection, a relationship best shown in the brain and skull. Though the endoskeletal tissues are relatively inactive as compared with the other body tissues, they are basically living tissues. And, by way of exception, it should be noted that a very active tissue is supplied in bone marrow.

Though wide variety exists in the types of tissue associated together in the endoskeletal system, yet, fundamentally, all of them are united in the possession to a greater or less degree of a characteristic structural material, collagen, lying between the connective tissue cells, which is formed as an intercellular secretion. Collagen is proteinaceous, typically fibrillar, and comparable in its wide distribution in the vertebrate body (but not in its chemical composition) to the ubiquitous carbohydrate, cellulose, of the plant world. The endo-

skeletal tissue system may appropriately be grouped under the term *collagenous*. Lying embedded in the collagenous ground substance of the connective and supporting tissues are the cells that appear to be primarily responsible for the synthesis and secretion of collagen. These cells, constituting the so-called fibroblasts, are typically seen in developing connective tissues as elongated spindle-shaped bodies, but both the structural and functional characteristics of the fibroblasts are subject to wide variation in the widely divergent types of endoskeletal tissues. (Figs. 19, 99.)

Fig. 99.—Bundles of collagenous fibers in ground substance of white fibrous tissue. Photomicrograph.

The embryologist studying the origin of the endoskeletal system in the embryo sees a unity throughout the various types of tissue as they gradually differentiate during development. The endoskeleton begins with a gelatinous type of embryonic connective tissue filling various cavities in the embryo between the germ layers. It continues with the formation of fibrous tissues in which distinctive bundles of collagenous fibers are abundantly present in the ground substance, as in white fibrous tissue or tendons. Later, cartilage appears in various regions, with a more rigid gel-condition of the intercellular material which may be either fibrous or homogenous in nature. Finally, bone tissue is formed largely by the transformation of the cartilage through the deposition of inorganic salts, notably calcium and phosphorus. Certain specialized types of connective tissue, as found in elastic and

adipose tissue, contain a considerable amount of collagen but seem to be outside the main routes of endoskeletal development that culminate in the formation of bone. Detailed consideration may now be given to the structural and functional features of bone as the culmination of

Synopsis of Skeletal Divisions

- Skeleton
  - Axial
    - Skull
      - Cranium
        - Brain case
        - Olfactory capsules
        - Auditory capsules
      - Visceral skeleton
        - Upper jaw
        - Lower jaw
        - Hyoid and larynx
    - Vertebral column (including ribs when present)
  - Appendicular
    - Girdle
      - Shoulder
        - Scapula, suprascapula, coracoid, procoracoid, epicoracoid, clavicle, episternum, omosternum, sternum, and xiphisternum
      - Hip
        - Ilium
        - Ischium
        - Pubis
    - Free limb
      - Arm
        - Humerus
        - Radio-ulna
        - Carpals
        - Metacarpals
        - Phalanges
      - Leg
        - Femur
        - Tibio-fibula
        - Tarsals
        - Metatarsals
        - Phalanges

Fig. 100.—The main divisions of the bony vertebrate skeleton. (*Reed and Young.*)

the endoskeletal system in man and all the vertebrates, with the exception of the cartilaginous fish.

Bony Skeleton

The bony skeleton shows wide variation in the different classes of vertebrates in accordance with the size of the body and the particular

environment for which a certain group is adapted. Thus the fish and other aquatic vertebrates are able to move freely in the water by a rhythmic back-and-forth movement of the body and tail, but this type of locomotor apparatus is of no use for air-living birds or for a bipedal and living vertebrate. Nevertheless, the basic resemblances of the vertebrate skeleton are much more apparent than the variations, which are of relatively minor importance. Thus all vertebrate

Axial skeleton	
Vertebral column:	
Vertebrae	24
Sacrum	1
Coccyx	1
Skull:	
Cranium	8
Facial portion	14
Neck and chest regions:	
Hyoid	1
Sternum	1
Ribs	24
Appendicular skeleton	
Forelimbs:	
Hands	28
Wrists	26
Arms	6
Shoulder girdles	4
Hindlimbs:	
Feet	28
Ankles	24
Legs	6
Kneecaps	2
Pelvic girdles	2
Total	200

skeletons are found to consist of two basic divisions: the axial skeleton, consisting of the skull and vertebral column; and the appendicular skeleton, consisting of the fore and hind limbs and their respective girdles, which connect the limbs to the axial skeleton. Furthermore, throughout the classes of vertebrate animals it is possible to homologize the bones associated with a particular region or organ in one animal with those present in widely varying animal types. Comparative anatomists have long regarded the vertebrate skeleton as one of the most favorable organ systems for the study of homologies.[1] (Plate XI; Fig. 100.)

The number of separate bones in the skeleton is subject to wide variation in the different vertebrate classes. The variation is partic-

[1] Consult Appendix: Comparative Anatomy.

ularly evident in the tail region and in the bones of the hands and feet. Many vertebrates of high development have a long caudal appendage, the tail. Thus, the cat, for example, has 22 vertebral bones in the tail. In the birds, the forelimbs are modified as wings instead of hands, and the number of bones in a wing has been somewhat reduced as compared with the typical pentadactyl appendage of man. The reduction of bones in the fore and hind limbs is even more evident in certain of the hoofed mammals (Ungulata). The horse, for example, retains only one functional digit on each of the four limbs. The number of bones in the adult human skeleton is usually given as 200, but 6 more bones may be added by including the 3 tiny ossicles in each ear. The distribution of bones in the skeleton of man is summarized on page 195.

Axial Skeleton

Vertebral Column.—One of the characteristics of the great phylum Chordata, to which man and the other vertebrate animals belong, is a longitudinal cylindrical rod, the notochord, situated near the dorsal surface of the body and continuing throughout the entire length. The notochord thus serves as a primary supporting axis. In the lowest vertebrates, the Cyclostomata, the notochord retains its original characteristics; but in the higher vertebrate classes with a bony skeleton, the notochord is replaced by a segmented vertebral column built up of individual vertebrae. In the more primitive types, each vertebra consists of a solid disc of bony tissue, the centrum, and these, placed end to end and held in place by ligaments of connective tissue, compose the segmented, rod-like vertebral columns for the general support of the body and the attachment of muscles. (Fig. 23.)

The vertebral column, seen in man and most of the vertebrates, has developed additional bony structures which are arranged to supply great protection to an essential portion of the nervous system, the spinal cord. The most important of the new structures of the vertebrae consists of a bony neural arch which develops dorsally from each centrum. The cavity between the arch and the centrum is the vertebral canal, a well-protected area in which the spinal cord lies. Projecting from each neural arch are the dorsal and lateral articulating processes which are of great importance in the articulation of separate vertebrae with each other in forming the vertebral column and also in their availability for the attachment of muscles. Thus the backbone, or vertebral column, is composed of independent articulated units, the vertebrae, each of which is essential in the support of the

body and each also contributes, by means of the neural arch, a portion of the common vertebral canal for the protection of the spinal cord. The vertebral column, as a whole, gives firm support to the major axis of the body and at the same time permits considerable freedom of movement. (Plate XI; Fig. 101.)

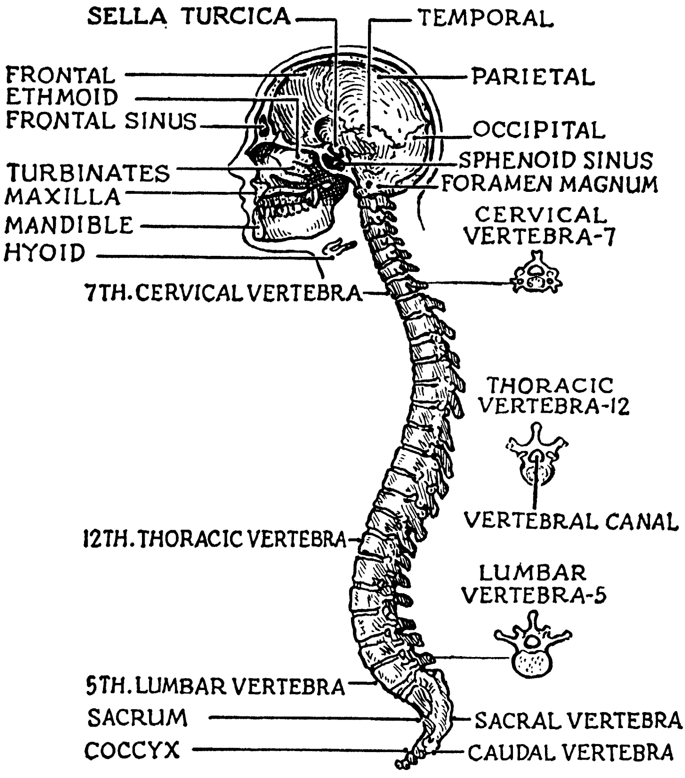


FIG. 101.—Skull and vertebral column of man, side view. End views of three vertebra are shown at the right. Skull is sectioned to show interior structure.

Five regions are recognized in the vertebral column of the higher vertebrates, which, beginning at the anterior end, are known as the *neck region* (cervical), *chest region* (thoracic), *abdominal region* (lumbar), *pelvic region* (sacral), and *tail region* (caudal). In the backbone of the human adult there are 26 vertebrae divided as follows: 7 cervical; 12 thoracic, with a pair of ribs attached to each; 5 lumbar; 1 sacral; and 1 caudal. In the early stages of development, 33 separate vertebrae are present. The vertebral reduction in the adult is due to a fusion of five sacral vertebrae to form one sacral (sacrum), and a fusion of four caudal vertebrae to form one caudal (coccyx).

Skull.—The vertebrate skull is an extraordinarily complex assembly of bone units designed to offer adequate protection to the most delicate organ of the body, the brain. The skull consists primarily of (1) a brain case, or cranium, enclosing the brain proper and also providing places of refuge for the important sense organs of the body —eyes, nose, ears—and (2) a facial portion built around the mouth and provided with a masticating apparatus which involves an intricate assemblage of bony parts and attached muscles. Studied compara-

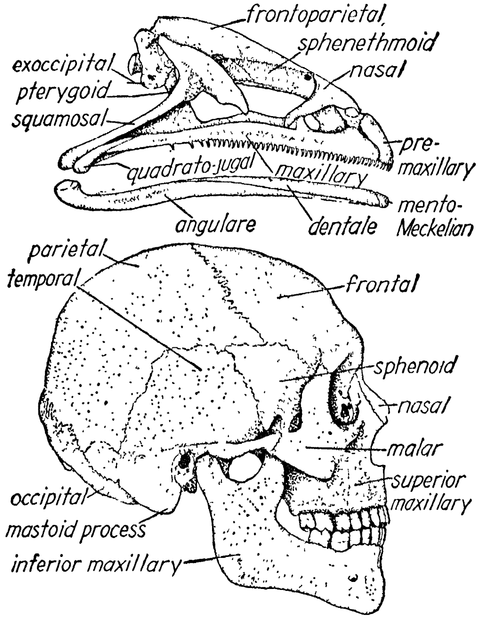


FIG. 102.—Comparison of frog skull and human skull. Side views. Human skull reduced to comparable size. (*Wieman.*)

tively, the skulls of the different vertebrate groups reveal considerable variety in the size relations existing between the cranial and facial portions. The skull of a lower vertebrate, as in the frog, shows a comparatively large facial portion and a very small cranium. The opposite condition, with a greatly reduced facial portion and a large cranium to provide adequate quarters for the enlarged brain, is seen to best advantage in the human skull. (Fig. 102.)

The 22 bones present in the adult human skull represent a considerable fusion of the bones originally present in the embryonic skull. The arrangement of the eight cranial bones forming the cranium may now be considered, beginning with the large unpaired occipital bone which forms the floor of the cranium. It is characterized by a large central

opening, the *foramen magnum,* through which the spinal cord enters the cranium and connects with the brain. The occipital bone is continued well up on the back of the skull where it joins a pair of large parietal bones which form the roof of the skull. Forming the ear region on each side of the head is a temporal bone. It is bounded posteriorly by the occipital, dorsally by the parietal, and anteriorly by the sphenoid; the latter, together with the small ethmoid, form the floor of the cranium anterior to the occipital region. The frontal bone, continuing anteriorly from the parietal, forms the forehead and, laterally, at about the level of the eye, joins with the sphenoid and ethmoid. (Fig. 101.)

In the facial portion of the skull the 14 constituent bones, well-covered with the muscles of the jaw and face, occur in pairs, with two exceptions. The exceptions are the single vomer, which separates the right and left nostrils, and the lower jaw, or mandible. The remaining six pairs of facial bones include, first, the pair of maxillae which form the upper jaw. The two members of the pair meet in the mid-line of the face and continue posteriorly as the hard palate, which forms the roof of the mouth and separates the mouth cavity from the nasal cavity just above. Also included are (a) the palatine bones which join with the maxillae posteriorly and continue the bony wall into the throat region; (b) the cheek bones (malar) which join with a maxilla bone on each side of the head, dorsally with the frontal and, posteriorly, with a projection of the temporal to form the zygomatic arch which articulates with lower jaw in the ear region; and, finally, (c) a pair each of nasal, lachrymal, and turbinate bones which together form the roof and side walls of the nose.

Teeth.—Strictly speaking, the vertebrate teeth are exoskeletal rather than endoskeletal structures, but their close association with the bony jaws makes it advisable to consider them in connection with the skull. Teeth are typically composed of (1) a thin outer covering, the enamel, which develops as a secretion from the invaginated epithelial cells of the mouth cavity lying over the jaws; and (2) dentine which develops from the underlying mesodermal tissue. The latter forms by far the greater amount of material in a tooth. In the center of the dentine area is a pulp cavity with vascular and nerve elements. Teeth in the various vertebrate classes are subject to considerable variation in number, shape, and function. In man and the higher vertebrates, a considerable portion of each tooth is embedded in a deep pit, or alveolus, in the jaw bone and firmly fastened by a bone-like cement substance. The portion of the tooth within an alveolus is known as the *root;* and the exposed, enamel-covered portion

is termed the *crown*. Four types of tooth are recognized in the human jaw, which, beginning anteriorly, are designated as the incisors, canines, premolars, and molars. (Fig. 27.)

Commonly two sets of teeth are formed. The first set, or milk teeth, are replaced in the early years of childhood by the permanent teeth which begin to develop in the jaws before the milk teeth are lost and erupt shortly afterward. The number of milk teeth varies somewhat, with a normal of 20, while in the permanent set there are 32 teeth, divided so that each half of each jaw contains a total of eight teeth, including two incisors, one canine, two premolars, and three molars. The third molars or wisdom teeth are frequently delayed in their appearance or fail entirely to erupt, with consequent abnormal conditions. In order to state concisely the number of teeth in the various animals, a dental formula is made use of, in which the letters *I*, *C*, *P*, and *M* are used to indicate the incisors, canines, premolars, and molars, respectively, and the numbers of each of these teeth in *half* of the upper and lower jaws are shown by figures above and below a division line. Thus the dental formula of man is shown as $I\frac{2}{2}$, $C\frac{1}{1}$, $P\frac{2}{2}$, $M\frac{3}{3} = 32$.

Neck and Chest.—Each of the 24 ribs may be described as a slender bone gracefully curved to form the circular chest wall. All of the ribs are attached dorsally to the transverse process of the corresponding thoracic vertebra. The anterior seven pairs of ribs are attached ventrally by means of a short strip of cartilage to a median unpaired dagger-shaped bone, the sternum, which forms the "keystone" of the thoracic arch surrounding the chest cavity. The eighth, ninth, and tenth pairs of ribs are also supplied ventrally with a terminal strip of cartilage, but the latter, in these ribs, is not connected directly with the sternum but with the cartilage of the rib just anterior. The ends of the eleventh and twelfth pairs of ribs have no ventral attachment but end freely in the muscle tissue of the body wall. In the neck region, a U-shaped hyoid bone lying just anterior to the larynx is without great functional significance in man, but great interest is associated with it from the standpoint of comparative anatomy because of its condition in the lower vertebrates. (Plate XI*A*, *B*.)

Appendicular Skeleton

The appendicular skeleton of man consists of the paired pentadactyl fore limbs and hind limbs and the girdles by which these appendages are attached to the axial skeleton. (Plate XI.)

Forelimb and Pectoral Girdle.—The arm bones consist, first, of a large humerus which articulates proximally with the shoulder girdle. The distal end of the humerus is in contact at the elbow with two bones, the radius and the ulna, both of which continue to the wrist (carpus). The wrist consists of an aggregation of eight small carpal bones, followed by the hand proper with its quota of 19 bones. Five of the hand bones (metacarpals), which are articulated with the bones of the wrist, are long and slender and form the undivided main portion of the hand. Finally, the five digits contain a total of 14 phalanges, with three for each of the fingers but only two for the thumb, which has one less joint. The shoulder, or pectoral girdle of man has only two bones. There is, first, the flat, dorsal shoulder blade, or scapula, which is firmly anchored in the shoulder muscles but not actually fused with the axial skeleton. The scapula is joined at the shoulder by the collar bone (clavicle). The latter is slender, rod-shaped and extends anteriorly to the head of the dagger-shaped sternum. Articulation between arm and girdle is by a special cavity, the glenoid fossa, into which the head of the humerus fits to form the shoulder joint. (Plate XI*A*.)

Hindlimb and Pelvic Girdle.—The bony structure of the leg is very close to that of the arm, but the names given to bones are different. There is, first, the large thigh bone, or femur which corresponds to the humerus of the arm and articulates at the knee with the tibia and fibula. The latter are homologous with the radius and ulna. An additional bone, the kneecap or patella, gives added protection to the important knee joint. In the ankle (tarsus) are only seven bones, one of which, the calcaneum, is very large and forms the heel proper. The other tarsal bones are closely assembled, so that only a slight amount of movement is possible, and fastened with ligaments in such a manner that the inner portion of a normal foot is elevated to form the arch. The flat-footed condition represents a harmful breakdown of the normal tarsal assembly. The five metatarsal bones form the body of the foot and extend to the base of the toes. As in the hand, there is a total of 14 phalanges in the digits, the big toe lacking one joint and the corresponding phalangeal bone. Compared with the fingers, the toes show a considerable reduction in length and in functional adaptability. And the big toe is not opposable to the other digits as is the thumb with the four fingers of the hand. Each pelvic girdle consists of a single bone (os innominatum) which represents a fusion of three embryonic bones. The pelvic girdle and the axial skeleton are firmly united by bone tissue in the sacral region of the vertebral column. A deep cavity, the acetabulum, is present in the

girdle, and this receives the proximal end of the femur, thus forming the ball-and-socket hip joint noted below. (Plate XI*A*.)

Variation in the Appendages of Vertebrates.—The paired fins of the bony fish do not appear at first glance to show much resemblance to the pentadactyl appendage but nevertheless are regarded as the original type from which the others have arisen. The greatest amount of variation between the legs and arms of vertebrates is found in the bones of the wrist and hand and those of ankle and foot. The three large bones, which form, the main axis of an appendage, are relatively constant in their structure throughout the vertebrate series. Thus even in a highly modified appendage, as

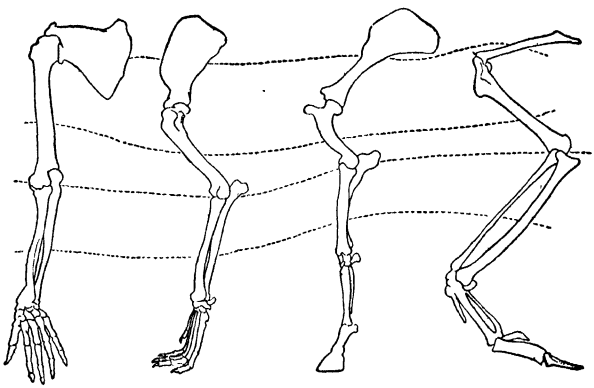


FIG. 103.—Comparison of the bones in the forelimbs of man, dog, horse, and bird. Dotted lines connect the homologous bones. Appendages are not drawn to scale. (*Watkeys, Stern.*)

found in the forelimb of the birds, the humerus, radius, and ulna remain essentially typical in their structure, but the bones of the wrist and hand region show marked structural modifications as well as a reduction in numbers, changes that better adapt them to the needs of a wing designed for aerial locomotion. (Fig. 103.)

In the hoofed mammals (Ungulata), both the fore- and the hindlimbs have departed more widely from the pentadactyl types than have those of most other vertebrates. Thus, for example, in the forelimb of the horse, the humerus is about the only bone that does not show wide departure from the typical condition. Only a small portion of the ulna remains, and it is fused with the radius. Digits I and V have entirely disappeared. Remnants of digits II and IV are present as vestigial structures, the splint bones. Digit III, essentially complete in its bony elements, is the only functional digit in both the fore- and hindlimbs, so that in locomotion the horse uses only the tip of the third digit, completely covered with the hoof. In the aquatic

mammal, the whale, both the hind limbs and the girdles have almost completely disappeared and are not functional, whereas the forelimbs have become modified for locomotion in water. Even more complete reduction in limb structure is seen in snakes, where a complete disappearance of all functional appendages has occurred in practically all species. The appendages of the primates, as shown in the description of the human appendages above, have remained true to the typical pentadactyl type, and only minor modifications and fusion of certain girdle bones and those in the arms and feet are in evidence. And so the vertebrate appendages are adapted for "all walks of life."

Joints.—The human skeleton shows various methods for the articulation of the 200 separate bones of which it is composed. In some places, as, for example, in the cranium, the bones are so rigidly articulated by toothed edges, which fit into corresponding depressions, that no movement between them is possible. In the vertebral column, a certain amount of flexibility is introduced between the separate vertebrae by the smooth articulating surfaces present on the bony processes of the neural arches which are nicely fitted to each other. In addition, pads of elastic cartilage are situated between the centra of the apposed vertebrae, which can be compressed in response to the bending movements of the trunk region. (Fig. 101.)

We now come to the articulating surfaces of bones which are definitely associated with movement of the appendages. Such articulations are known as *joints*, and several distinct types may be indicated. The least differentiated type of joint and one that affords comparatively little opportunity for movement is the gliding joint found in the bones of the wrist and ankle. The articulating bones are fastened so closely by connective tissue ligaments that only a slight gliding movement is permitted. Much better developed are the hinge joints of the fingers, toes, and knees, which permit a wide latitude of back-and-forth movement in the same plane, like the swinging of a door. The very important hinge joint in the knee is protected by an additional bony element, the kneecap (patella). A modification of the hinge joint which permits rotation of the hand, in addition to the back-and-forth movement, is found in the pivot joint at the elbow. The radius and ulna are so articulated with the humerus at the elbow that, when the palm of the hand is turned up, the distal end of the radius revolves around the ulna, thus following the thumb as it changes position. (Fig. 87.)

The ball-and-socket type of joint permits the greatest freedom of movement. It is best shown in the large hip joints which are able to support the weight of the body and also a considerable additional

weight when necessary; at the same time the hip joints permit the varying leg movements essential to locomotion. In the hip joint is an airtight fit between the almost spherical head of the femur and the deep socket, acetabulum, in the pelvic girdle. The fit is so perfect that, even with all the connecting ligaments removed, the femur will be held in place by the atmospheric pressure. Ball-and-socket joints of lesser degree are found in the articulation of the humerus with the shoulder girdle and also between the metacarpal bone of the thumb

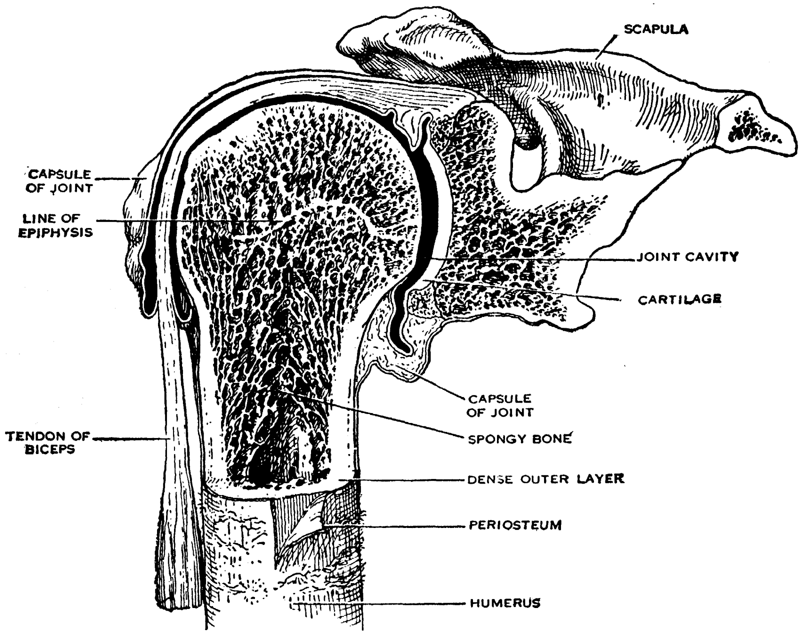


FIG. 104.—Section through the shoulder joint of man. (*Haggard, "Science of Health and Disease," Harper & Brothers.*)

and the wrist. This ball-and-socket thumb joint permits this important digit to be placed in opposition to the ends of the other digits. This movement is not present in the less adaptable foot, where the big toe has only a hinge, rather than a ball-and-socket, joint. The articulating surfaces of the hinge and ball-and-socket joints, in which bone movements are extensive, are covered with a layer of smooth hyaline cartilage. In addition, the cartilaginous surfaces which are in contact are in turn covered by a very thin synovial membrane supplied with secreting cells that continually secrete a synovial fluid for joint lubrication. (Fig. 104.)

Finally, mention should be made of a modified pivot joint, forming the connection between the head and the vertebral column, which per-

mits wide latitude in head movements. The occipital bone at the base of the head bears two smooth articulating surfaces, the occipital condyles, near the *foramen magnum.* The first vertebra (atlas) articulates with these to give back-and-forth movements. In rotary head movements, the atlas is aided by the special odontoid process of the second vertebra (axis) which extends upward through the atlas and functions as a pivot or the rotary movements of the head and atlas.

Development of Bone.—Bones develop as a result of the deposition of inorganic salts in the original soft skeletal elements. Two types of bones are recognized. First there are membrane bones that are formed by the gradual transformation and hardening of soft connective tissue membranes as typically form the basis for the membrane bones of the skull. Outside of the skull bones, however, practically all of the bones in the human skeleton arise as modifications of cartilage and are, therefore, known as *cartilage bones.* It sounds simple enough to say that connective tissue membranes and cartilage are transformed into bone, but, as a matter of fact, the chemical and structural changes necessary for such a transformation are very complex and not fully explained as yet. Two types of bone-forming cell are involved. One type, the osteoblasts, is able to absorb the needed inorganic salts from the blood stream and to use them in the building of bone tissue. The other type of bone cell, the osteoclasts, is charged with the duty of remodeling the original connective tissue model to conform to the new bone-tissue requirements. This remodeling involves the actual destruction of certain portions of the original cartilage, presumably by the use of specific enzymes. In this way, the central cavity of bone, which contains the highly vascularized bone marrow, is formed.

It must be remembered, too, that the tiny bones, as first laid down in the embryo, must increase in size to correspond to the general body growth, and this growth of the bones must continue until maturity is reached. Increase in the length of a bone occurs principally at each end, where new cartilage is continually being formed and, then, gradually ossified. Growth also occurs at the bone surface through the action of an outer connective tissue covering, the periosteum, which supplies bone-forming cells and also the materials for the formation of new bone tissue. The periosteum continues, when necessary, to function in this manner throughout life, as in the case of bone fractures. The general size and shape of a bone, as well as its microscopic structure, reveal a high degree of adaptation to the exact functional needs of the region in which it is found. This is not merely a passive relation, for bones continue to change all through life in accordance with the structural needs that develop.

The examination of a typical bone, such as the long thigh bone (femur) of the leg, shows that it consists of a main portion, or shaft (diaphysis), with a terminal enlargement at each end which forms the articulating surfaces, or joints, with the connecting bones. The joints as noted, are covered with a smooth cartilage which affords the best possible type of all the tissues for articulating surfaces. The cartilage at the joints never becomes ossified. The entire bone, with the exception of the articulating surfaces, is covered by a closely applied sheet of specialized connective tissue, the periosteum, which was mentioned above in connection with bone formation and regeneration. It can be shown that bunches of the connective tissue fibrils from the periosteum penetrate deeply into the underlying bone tissue. This penetration of various functional tissues by an outer layer of connective tissue is characteristic also of the muscles and nerves. (Fig. 89.)

If the femur is split in halves lengthwise, it will be found that the bone is hollow throughout almost its entire length and, therefore, the bony tissue really consists of a relatively thin outer shell surrounding a central cavity. This is the marrow cavity, filled with the soft pinkish bone marrow and abundantly supplied with blood vessels and nerves. Bone marrow functions not as an endoskeletal tissue but as a vascular tissue primarily concerned with the formation of red blood cells. The marrow cavity is also lined by a layer of connective tissue, the endosteum. An examination of the cut surface of the bone tissue will show, even with the naked eye, that there is a differentiation into a compact bone tissue forming the walls of the shaft and a so-called spongy bone tissue at each end. In the spongy tissue, the bone fibers can be seen extending in various directions, crossing and supporting each other. Careful study of the arrangement of the bony fibers in the spongy bone tissue shows very clearly that they are arranged according to the best engineering principles to give the utmost strength with the least use of material. These same excellent engineering features apply to the bone as a whole. (Fig. 104.)

Histology of Bone.—The microscopic examination of bone tissue reveals an extraordinarily intricate arrangement of the intercellular matrix forming the mass of bone tissue, with embedded bone cells and a puzzling array of interconnecting channels of various kinds and sizes. The complexity of mature bone is particularly striking when it is compared with the very simple arrangement of the cartilage elements from which it develops. In order to study bone tissue under the microscope, it is necessary to take small fragments and carefully grind them down by hand until they are thin enough to be transparent. After grinding, the bone fragments can be mounted on a slide for

detailed examination. Under the low power of the microscope, considerable structural differentiation in the bone tissue is apparent. The general picture of bone structure, as revealed under the microscope, reminds one somewhat of the cyclonic areas in a weather map with concentric lines curving around the low-pressure areas. (Fig. 105.)

The curved areas in the bone tissue are the lamellae and consist of concentric layers, or plates, of bone tissue. In the center of each of these areas of bony tissue, as seen in a transverse section, is the circular opening of the Haversian canal, measuring about 0.002 in. in diameter.

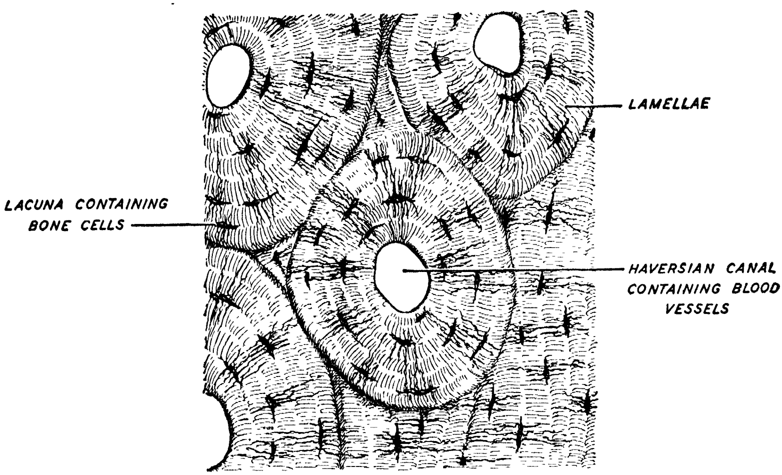


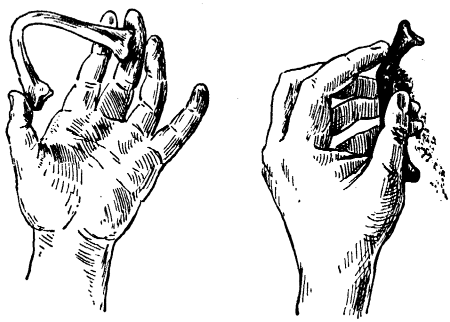
FIG. 105.—Microscopic structure of bone. (*Buchanan, "Elements of Biology," Harper & Brothers.*)

For the most part, the Haversian canals run lengthwise of the bone, but connecting canals, extending transversely, are also found, some of which continue to the surface of the bone tissue and open underneath the periosteal covering. Altogether the Haversian canals form a ramifying tubular network throughout the bone tissue in which the blood vessels extending from the periosteum can enter and supply all regions of the bones.

The examination of bone under a higher magnification reveals additional important structural elements. Many tiny cavities (lacunae) are revealed, each containing a living bone cell (osteoblast). Extending from each lacuna are many exceedingly minute channels which pursue irregular winding courses through the bone tissue and open either directly into one of the large Haversian canals or into other canaliculi that so open. Thus blood plasma, exuded from the tiny vessels in the Haversian canals, is carried by the connecting canaliculi to all the bone cells. It is estimated that areas of bone tissue exceed-

ing 0.00004 in. in diameter are not found without being supplied with blood by a canaliculus. Directly under the periosteum, the lamellae and accompanying canals encircle the bones to form rings of bony tissue rather than longitudinal elements.

It is apparent from the description just given that bone tissue is a living tissue with many cells and a network of large and small channels for the distribution of the essential materials. By placing a piece of bone in a weak acid for a time, it is possible to remove the calcareous bone materials and leave the organic collagenous material which always



A *B*

Fig. 106.—Comparison of bone which has been soaked in acid (*A*) and bone which has been burned (*B*).

forms the underlying framework. A bone treated with acid is flexible and can be tied in a knot without breaking. On the other hand, if a bone is burned, the organic materials will be destroyed and the inorganic materials will remain in their original shape if undisturbed. Burned bone is very fragile and will crumble to dust when handled. (Fig. 106.)

Nowhere is the living character of the bony endoskeleton so clearly revealed as in the highly important bone marrow, which serves as a specialized tissue, largely concerned with the formation of the red cells of the blood. Bone marrow also functions in fat storage and is usually separated into the red marrow, in which the blood cells are formed, and yellow or fatty marrow in which fat accumulates. No clear histological difference exist between the two types, and a shift from one to the other may occur. Histologically, bone marrow consists of a connective tissue ground substance, or stroma, containing quantities of cells specialized for red cell formation, as well as fat-storage cells. Penetrating throughout the marrow tissue are open blood channels, or sinusoids, such as were previously noted in the liver. Since the

sinusoids lack a definite wall as present in capillaries, newly formed, nonmotile red cells are able to pass directly into the circulating blood as the latter slowly moves through the sinusoids of the bone marrow. Small blood vessels enter and leave the bone by way of the periosteum and Haversian canals, but the blood supply of the bone marrow is received directly by large vessels which penetrate the bone tissue by definite openings, the foramina.

FUNCTIONAL FEATURES ASSOCIATED WITH THE SKELETAL SYSTEM

The skeletal system is commonly thought of as being wholly concerned with the functions of protection, support, and muscle leverage, but at least two other functional features of this system are inseparably associated, namely, the formation of the blood cells in the bone marrow and the storage of calcium by the bone tissue. These five functions may now be considered in the order named.

FIG. 107.—Illustrating the relations between the functions of protection and support in the skeletal system. In the higher animals (right) the support becomes increasingly important. (*Walter.*)

Protection and Support.—Protection of the delicate tissues and organs is primarily a function of the exoskeletal elements. This is particularly evident in such invertebrates as the clam and the insect. The function of support for the body tissues appears as the major function of the vertebrate endoskeleton. Thus, broadly speaking, relatively less protection is offered to the living tissues of the higher animals than to the lower types. In man, the greatly reduced exoskeletal elements offer a minimum of protection, the living tissues being mostly covered by a few layers of epithelial cells. However, the structural development and functional importance of the central nervous system require that it be well protected, and this has been accomplished by the bony endoskeleton as was indicated above in the study of the skull and vertebral column (page 196). And so the endoskeleton, primarily functioning for support, has also been assigned the protection of the central nervous system, the most important and delicate structure in the vertebrate body. (Fig. 107.)

Movement.—The adaptation of the bones and associated connective tissues in the various vertebrate types, so as to serve with the contractile muscle tissues in providing for the numerous essential body movements and for efficient locomotion in water, in air, or on land, has reached great heights in the higher vertebrates but nowhere to so marked a degree as in the human skeleton. This skeletal superiority is largely centered in the human arm and hand, in which the combination of skeletal, contractile, and nerve elements has made an

unrivaled living tool capable of coping with the myriads of duties that man finds necessary. It is also apparent in the skeletal changes in legs and bony girdles that make two-legged, bipedal, locomotion possible. A difference exists in the skeletal requirements for movement in an organ that remains stationary as compared with the requirements in which a part of the body is moved to a new location. Thus the involuntary muscles present in the ducts of glands, the alimentary canal, and the walls of blood vessels require only flexible fibrous tissues for support and leverage and for binding them into compact functional units adapted for the stationary movements associated with these organs. The voluntary muscles, on the other hand, move a finger, a foot, an arm, a leg, or the entire body to new positions, and the movements may be very rapid. Necessarily associated with these voluntary contractile tissues are the hard bones and also the mediating flexible fibrous tissues, the complete skeletal assembly being continuous from the sarcolemma of the individual muscle fibers to the immobile bone at the muscle origin and the movable bone at the muscle insertion which serves as a lever for the muscle pull.

Bones and Levers.—The physicist recognizes three types of rigid rods or levers that are available for leverage. These mechanical aids are commonly known as levers of the first, second, and third class. The classification depends upon the relative positions of three points on the lever: (1) the fixed point of support or attachment (fulcrum), (2) the point at which force is applied to move the lever, and (3) the point where work is accomplished. In levers of the first class, the fulcrum is situated between the other two points, as seen, for example, in a pair of scissors.

Two examples may be selected to show the use of bones in the body as levers of the first class. Thus, when the foot is lifted and the toes tapped on the floor, the ankle joint is the fulcrum; the pull of the large gastocnemius muscle in the calf of the leg is transmitted to the heel bone (calcaneum) back of the fulcrum; and the point of resistance, where the weight is moved, is the portion of the foot anterior to the ankle joint fulcrum. Another example is found in the movements of the head in which the atlas serves as a fulcrum, lying between the insertion of the muscle to the occipital bone above and the origin below (page 188). In levers of the second class, the fulcrum is at one end of the lever, the force is applied at the opposite end, and the weight is between the other two points, a condition that is well shown in a nutcracker. An instance in which bones are used as levers of the second class is seen when the weight of the body is raised on the toes. In this case, the fulcrum is at the solid surface on which the toes are supported; the work is accomplished at the ankle joints where the

body weight is supported; and the force is applied dorsally at the calcaneum by the contraction of the gastrocnemius muscle as in the first example. In levers of the third class, which sacrifice power for speed, the fulcrum is at one end of the lever, and the weight at the opposite end so that the force is applied between fulcrum and weight. The author notes as he writes that this is the method used in mounting the type bars of the typewriter, which are designed to move a small weight rapidly. Examples in which bones are used as levers of the third class are well shown in the arms where the pull of the biceps muscle transmitted to the insertion below the elbow joint elevates the

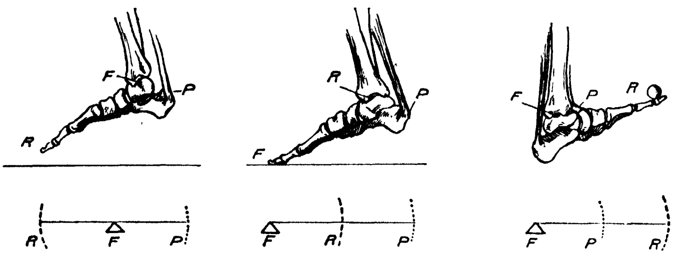


Fig. 108.—Illustrating the uses of bones in the three kinds of levers as described on page 210. *R*, resistance or weight moved; *F*, fulcrum; *P*, point at which power is applied from muscle contraction. (*Redrawn from Huxley-Barcroft.*)

forearm. The same arrangement is also seen in the extension of the leg by the pull of the ventral thigh muscles which is transmitted through the kneecap to the point of insertion below the knee. (Figs. 87, 108.)

Bipedal Locomotion.—Generally speaking, voluntary movements in animals are associated with locomotion, and, in the various groups, the locomotor organs present wide variation in structural design in order to function efficiently in water, in air, or on land. It would seem that the two most difficult conditions to surmount in animal locomotion are flight through the air and bipedal locomotion on land by man, birds, and to some extent by a few of the higher primates. Bipedal locomotion involves the maintenance of the trunk and head of the body in an upright position, the shifting of the entire weight to the hind limbs, thus freeing the forelimbs for other duties. It has been indicated in the previous chapter that the delicate balance essential to the maintenance of the upright position requires that certain muscles be kept in tone in agreement with the proprioceptive impulses received by the central nervous system from the outlying regions (page 184). More attention will be given to the nerve control involved in the erect posture in the following chapter. At present we are concerned with the complex harmony of action between the

muscle and bone elements in human locomotion, a function that is learned after much effort in early childhood.

Walking involves many muscles of the trunk and legs. When one starts to walk, the body is inclined or really begins to fall forward, which brings the center of gravity beyond the feet. Then one of the legs, say, the left, is flexed at the knee joint. This raises the left foot from the floor, and it is quickly thrust forward to support the falling body. Synchronously with the forward movement of the left leg, the gastrocnemius muscle in the calf of the right leg contracts and elevates the body by the pull on the heel bone, as noted in the previous paragraph. Then the left foot is firmly planted in its new position. At

FIG. 109.—Walking. Both feet on the ground.

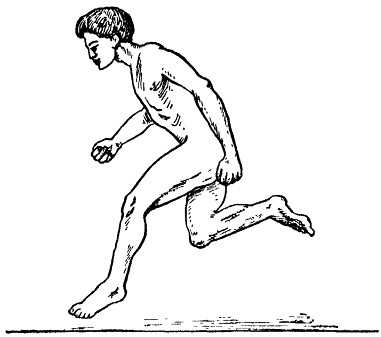


FIG. 110.—Running. Both feet off the ground.

this moment both feet are on the ground. When both feet are in the air at this position, the person is running rather than walking. The weight of the body is now shifted to the left leg, and this leaves the right leg free to swing forward, like a pendulum, to a new position in advance of the left leg. When the right leg is placed in position, the weight of the body is shifted to it, and the pull of the muscles is now on the heel of the left leg. The elevation and flexion of the latter enable it to swing forward in a pendulum-like motion and to come to rest once more in advance of the right leg. And so the coordinated alternate leg motions continue. (Figs. 109, 110.)

Blood-cell Formation.—With regard to the formation of blood cells by the bone marrow, the concensus of opinion at the present time seems to be that the tissues of the bone marrow always contain large numbers of a special amoeboid type of cell, the hemocytoblast, which is regarded as the basic type, the mother cell, so to speak, of red cells and also of the various types of granular leucocytes. As to how the differentiative processes are carried out through the many intervening cellular stages, very little information is available. The end result, namely, the production of an abundance of red cells and granular

leucocytes by the blood-forming, or myeloid, tissues of the bone marrow, is an established fact. Apparently the spleen is the only other tissue in the body that is equipped to play any part in the development of the blood cells. (Fig. 111; page 166.)

Mineral Reserves.—It is only in recent years that the function of the bones as a storehouse from which the calcium content of the blood may be kept at normal levels has been realized, though it was earlier recognized that regular calcium deposition was imperative for normal bone development in children. Abnormalities in the calcium metabolism of the developing bone tissue were first found to be responsible for rickets. And then it was shown that a deficiency of

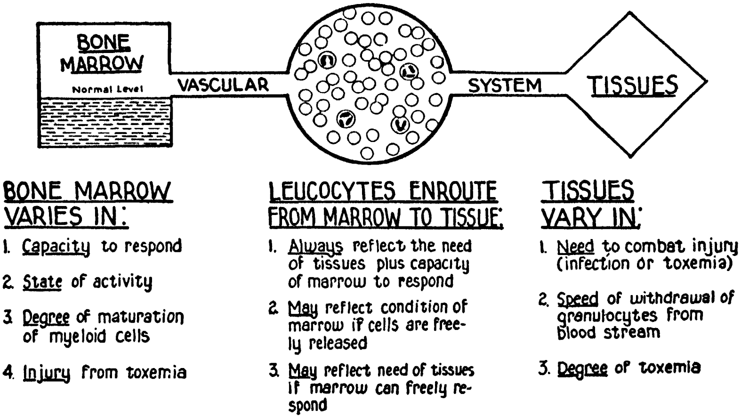


FIG. 111.—Illustrating the formation of blood cells in the bone marrow (left) and their utilization in the body tissues (right). (*Haden, "Principles of Hematology," Lea & Febiger.*)

vitamin D was at the basis of the abnormal calcium reaction in the bone tissues (page 60). The basic importance of free calcium in the blood plasma, however, was not realized until much later, when the experimental studies on the parathyroid gland showed that the hormone secreted by this gland was an essential factor in the maintenance of the normal amount of calcium in the blood (page 109). Furthermore, as noted previously, the absence of calcium from the blood very quickly produced other disastrous effects in the organism, primarily associated with increased muscle-nerve irritability, that, if not remedied at once by supplying calcium, were invariably fatal. Linked in the complete picture of blood calcium is the little-understood relationship between phosphorus and calcium. In some unknown way, these two elements work together to maintain normal conditions in the blood stream and are apparently deposited in the bone or removed from it as the conditions demand in order to maintain the normal levels in the blood stream.

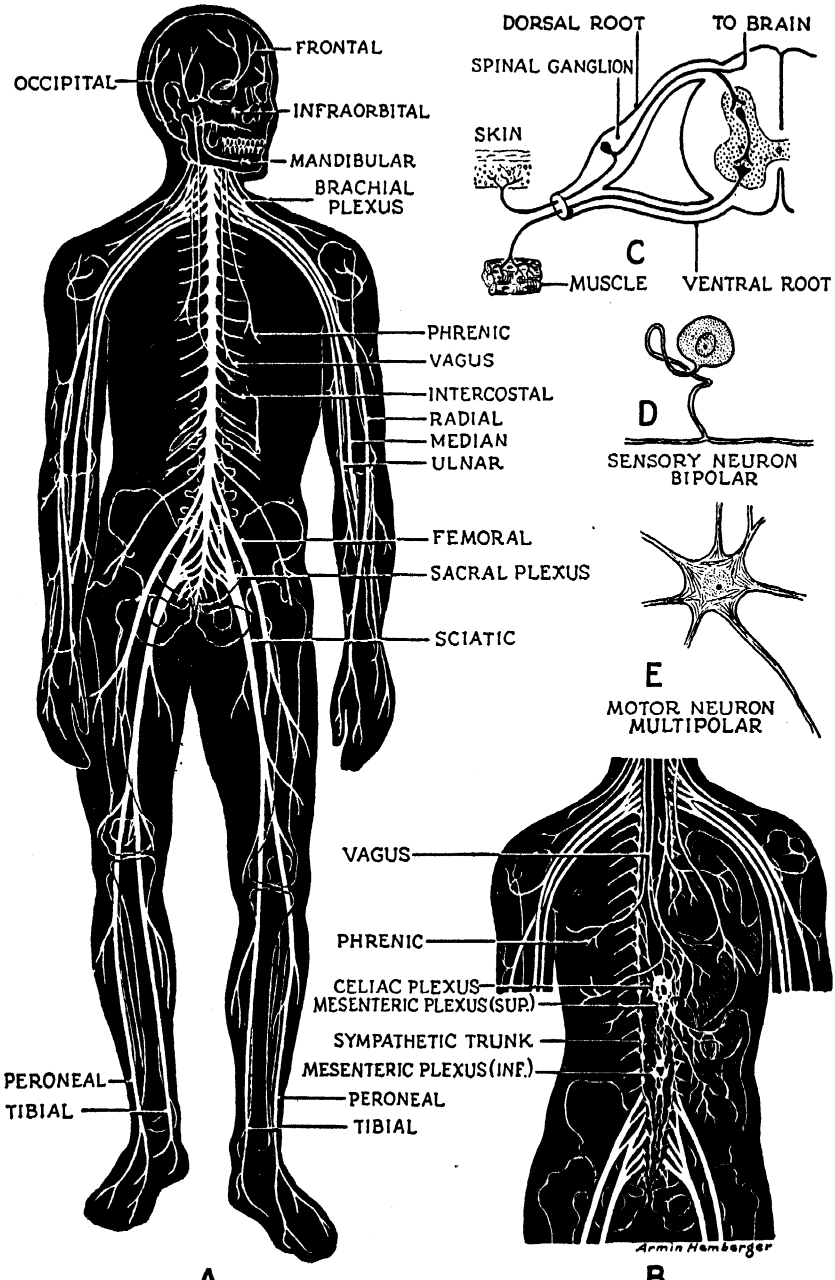


Plate XII.—Nervous system in man. *A*, illustrating the general plan, with the spinal cord and the chief nerve routes to the arms and legs; *B*, the chief components of the autonomic system; *C*, elements of the reflex arc; *D*, bipolar neuron; *E*, multipolar neuron. Diagrammatic.

CHAPTER X

BIOLOGY OF THE NERVOUS SYSTEM (I)

The nervous system as the master organ system of the body dominates the entire organism. It receives and interprets external stimuli which make known the environmental factors and also internal stimuli which reveal the conditions of the various organs. In order to do this, there are located at strategic points various types of sensory cells which are capable of receiving the particular stimuli, and the latter incite nerve impulses which travel into the central nervous system over the cable-like conducting nerve fibers. The central nervous system receives the impulses from the peripheral sensory areas, interprets the data, and then incites outgoing impulses which are transmitted over a separate set of nerve fibers to the motor tissues and cause coordinated action of these effector organs. Thus the basic function of irritability, which is common to all living matter, is largely assigned, in the multicellular animals, to the nervous system, and the extent of the assignment increases in the higher types in correspondence with the augmented tissue differentiation. In addition, the higher functions of consciousness, memory, intelligence, and volitional thinking come into more and more prominence and, finally, reach their full flowering in the human brain.

In order to receive the sensory impulses and to control and coordinate the activities of the muscle tissues and, as a matter of fact, all the tissues of the body as well, the nervous system must have direct connections through definite nerve fibers with all of the cooperating organ systems, with all of the constituent tissues, and, in many instances, as in the outlying sensory structures, with the individual cells. In a highly differentiated animal, it is easy to see that the sum total of all these nerve elements supplying every type of body structure necessitates the presence of an exceedingly intricate organ system—far beyond anything encountered in the previous studies of the other organ systems.

STRUCTURAL FEATURES ASSOCIATED WITH THE NERVOUS SYSTEM

From the comparative standpoint, specialized nerve cells, which mark the beginning of nerve tissue in the multicellular animals, are

first encountered in hydra and the related coelenterate animals. In these lowly metazoa, the nerve cells are not associated to form a definite tissue but appear as separate branched cells or as a diffuse nerve net, connecting directly with near-by contractile elements in the body wall. Each nerve cell is thus an independent functional unit for the reception and transmission of stimuli. A more advanced but still comparatively simple animal type, as seen in the earthworm, reveals important advances in the structure of the nerve elements. A definite nerve tissue is built up of associated cells and fibers with a differentiation into a central and a peripheral division, so that the principle of a central adjustor mechanism to mediate between the incoming sensory impulses from the receptors and the outgoing motor impulses to the effectors is early introduced into the animal organism, a development that, it may be said, persists throughout the higher types up to man and becomes of increasing importance. (Figs. 112, 113.)

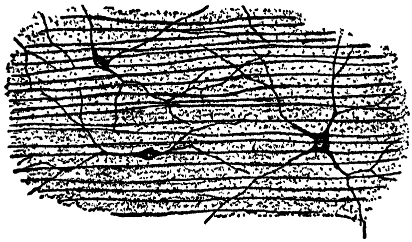


FIG. 112.—Nerve cells in the body wall of Hydra. The long fibrils in the stippled background represent contractile elements from the epitheliomuscular cells. (*Shull, after Schneider, slightly modified.*)

It will not be necessary to pursue the field of comparative neurology to greater lengths at present, except to indicate one or two basic structural differences between the invertebrate and vertebrate nervous systems. Thus, in the invertebrates, the central nervous system is seen to be extended throughout the length of the body as a ventral nerve cord, lying in the body cavity close to the body wall. In the vertebrate animals, the central nerve cord is dorsal in position, has a central cavity, and, in all except the most primitive vertebrates, is enclosed by the bony neural arches of the vertebral column as revealed earlier (page 196).

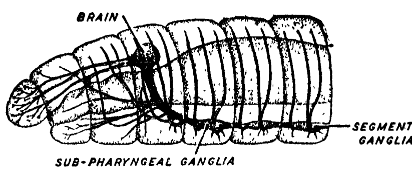


FIG. 113.—Nerve tissue in the anterior end of the earthworm. Shown are: the ventral nerve cord with segmental ganglia lying under the alimentary canal; the sub-pharyngeal ganglia where the nerve cord divides to form a nerve collar which encircles the pharynx and bears the dorsal brain. (*Buchanan, "Elements of Biology," Harper & Brothers.*)

Very early in its development, the vertebrate embryo begins to form a nervous system which in a short time enables it to keep in touch with the environment and to perform essentially adaptive responses. The first indications of the embryonic nervous system

are seen in a thickening and later infolding of the outer ectoderm on the dorsal body surface. In this way, which will be described in more detail later when the problems of embryology are considered, a hollow ectodermal tube is formed, extending the length of the body. As the ectoderm grows over the invaginated region, the tube comes to lie just beneath and entirely separated from the outer ectoderm from which it was formed shortly before. The walls of this primitive nerve tube, which is the forerunner of the nervous system, increase in thickness, and the anterior end soon undergoes radical structural changes which result in a definite delimination of the forebrain, mid-brain, and hindbrain and the further modification and subdivision of

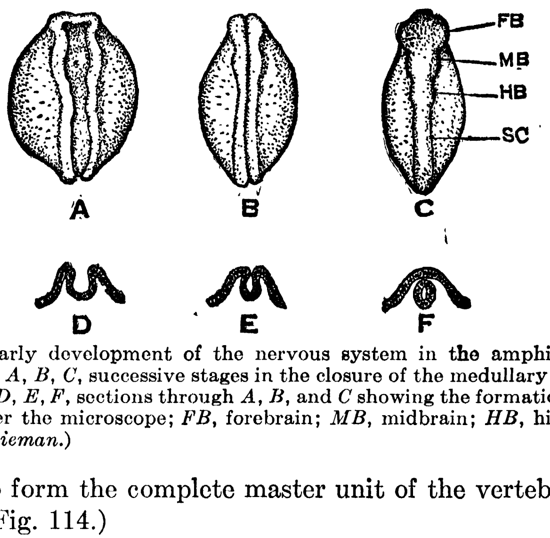


FIG. 114.—Early development of the nervous system in the amphibian embryo (Amblystoma). *A*, *B*, *C*, successive stages in the closure of the medullary folds to form the neural tube; *D*, *E*, *F*, sections through *A*, *B*, and *C* showing the formation of the tube as observed under the microscope; *FB*, forebrain; *MB*, midbrain; *HB*, hindbrain; *SC*, spinal cord. (*Wieman.*)

these parts to form the complete master unit of the vertebrate body, the brain. (Fig. 114.)

From the nerve cells (neurons) of this newly formed neural tube, microscopic cell processes, the nerve fibers, rapidly develop and soon connect all parts and tissues of the developing embryo. These fibers are primarily concerned with the conduction of the sensory nerve impulses coming in from the peripheral regions and the motor impulses going out to the contractile tissues. And so the embryo is soon in possession of a functional nervous system, comparatively simple at first but increasing in complexity as the rapidly differentiating tissues of the embryo continue to make new demands.

As finally constituted, the nervous system of man and other higher vertebrates can be separated for convenience in description into four major structural divisions as follows: (1) sense organs, or receptors, which are the outlying units specialized for the reception of external and internal stimuli; (2) peripheral nervous system with its network

of nerve fibers which innervate all regions of the body and function in conduction, involving the transmission of nerve impulses to and from all parts of the body; (3) autonomic nervous system, essentially a part of the peripheral nervous system in that it conducts impulses to and from the body structures that it innervates, but, as will be seen later, it is also associated with the involuntary control of various important organ systems; (4) central nervous system which serves as the integrative and controlling unit of the nervous system—from the structural standpoint, its complexity is unrivaled. In our present consideration, it seems logical to begin with the outlying sensory elements, then pass to the conducting elements of the peripheral system, and, finally, conclude with the master units of the central nervous system. (Plate XII.)

Sense Organs

It is customary to recognize five primary senses in the animal organism, namely, touch (including pressure, temperature, and pain), taste, smell, sight, and hearing. To these should be added the sense of position, or equilibrium, and those internal sensory phenomena, such as hunger and thirst, which enable the organism to determine its own internal conditions. The various sense organs, associated with the primary senses, function only as extremely sensitive receptors. Stimuli arise in them that result in the transmission of nerve impulses to the central nervous system, and the latter interprets the stimuli and determines the action to be taken.

Sense organs throughout the body, generally speaking, are composed of essential and accessory parts. The essential element consists of the specialized sensory cells or terminal arborizations which are capable of responding to a certain type or types of stimulus that impinge upon them in their particular peripheral location. Also generally present in the various sense organs are accessory structures that aid in bringing the stimuli to the sensory neurons. For example, the lens of the eye is an accessory structure which focuses the light rays on the sensitive nerve cells of the retina, the latter constituting the essential part of the eye. It should be kept in mind that the sense organs of the body are internal (interoceptive) as well as external (exteroceptive). Thus, the sensations of hunger and thirst have their origin in interoceptive sense organs scattered through the tissues of the body. The structural features of the internal sensory apparatus are not apparent, but those of the various external sense organs are well-known. Finally, sense organs are general or specific in their reactions to stimuli. In the first case, as seen in the skin, a

variety of sensory elements is subject to influence by different types of stimuli. In the specific type of sense organ, as seem in the eye, the neurons are capable of responding to one type of stimulus only—that received from the light rays. (Figs. 98, 126.)

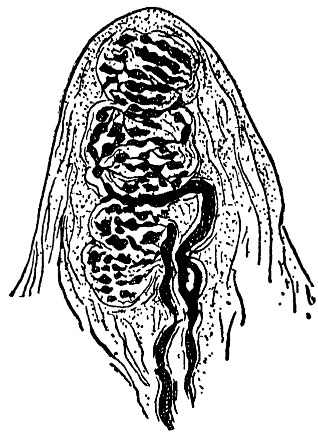


FIG. 115.—Tactile corpuscle in the skin of man. Highly magnified. (*Mitchell.*)

Skin Sensations.—Sensory elements located in the skin respond to a considerable variety of environmental stimuli, notably pressure (touch), temperature (heat or cold), and pain. Scattered through the skin just under the epidermis are numerous tactile corpuscles, each covered by a connective tissue sheath which contains the essential network of delicate nerve fibers and their endings. The tactile organs are sensitive to pressure or touch, as we commonly say. They are more highly differentiated and more abundant in the skin covering the tips of the fingers and toes than in other regions of the body. By testing very small areas of the skin surface with a fairly stiff hair mounted on a handle, it is possible to determine the distribution of these tactile areas. It will be found that, in the middle of the back, points separated by less than 2.7 in. (68 mm.) will be felt as a single stimulus. Points less than half this distance apart can be felt as separate stimuli on the back of the hand, whereas on the tips of the fingers, areas around 0.1 in. in diameter are felt as separate points of stimulation. Each hair follicle has sensory nerve endings that are very sensitive to contact, and less pressure is required to stimulate them. Even the slightest manipulation of a single hair is noted. (Figs. 24, 98.)

Temperature sensations and pain are received by separate nerve elements in the skin so that, altogether, four different sensory areas are found (pressure, heat, cold, and pain). There is some doubt as to whether or not pain should be regarded as a separate sensation. It is possible that excessive stimulation of any sensory nerve will give the sensation of pain. With the exception of the tactile corpuscles, noted above, sensory nerves in the skin do not terminate as definite sensory bodies, but each splits into a branching group of fibrillae (arborization) which lie between the epithelial cells. (Fig. 115.)

The nerve elements in the living tissues of the body are sensitive to chemical agents, and, as we have seen earlier, slight changes in the

chemical composition of the blood, due to variations in the carbon dioxide content, are detected and result in definite reactions to maintain the proper balance. The neurons associated with the sensations of taste and smell are, however, specialized for the reception of external chemical stimuli. In the epithelium of the tongue and nasal cavities, these chemical receptors are grouped to form highly developed sense organs. Attention was given to the taste buds of the tongue epithelium in an earlier chapter (page 44). Accordingly, attention may be given at once to the sense of smell (olfactory sense) localized in certain regions of the nasal epithelium. (Figs. 27, 116.)

Olfactory Sense.—A microscopic study of the olfactory epithelium shows an underlying layer of connective tissue bearing the sensory epithelial cells. The latter contain three cellular types: olfactory, basal, and interstitial. The olfactory cells are the functional sensory

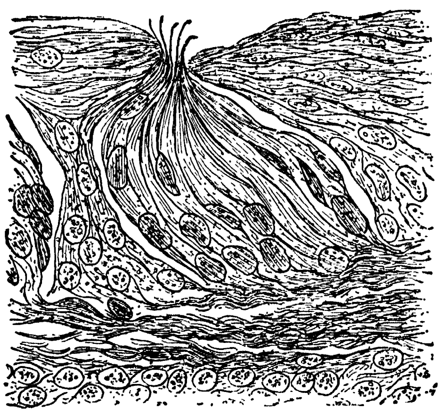


FIG. 116.—Section of taste bud of tongue. Highly magnified. (*Mitchell, after Ranvier.*)

neurons, situated between the interstitial cells. Each sensory neuron is an elongated cell, lying below and at right angles to the surface epithelium. The proximal ends of the olfactory cells, lying next to the connective tissue layer, connect with a very fine nerve fiber which is continuous with the conducting elements of the olfactory nerve extending to the central nervous system. The opposite end of each olfactory cell lies at the outer surface of the epithelium and splits into a terminal group of projecting olfactory cilia which are sensitive to chemical stimuli or odors present in the incoming air. The entire surface of the olfactory epithelium, bearing the exposed cilia, is kept continually moistened by secretions of the olfactory glands. The latter lie in the basal connective tissue layer and open through separate ducts at the surface. This secretion, of course, comes into direct contact with the chemical substances in the air currents and with the

cilia. It probably acts as a solvent for the volatile substances detected by the sensory cells. (Fig. 117.)

The sense of smell is unbelievably acute. It is known that a strong odor, such as that of vanillin, can be detected in a dilution of 1 part in 10 million, which is a far more delicate reaction than can be performed by the chemist. It is also certain that the olfactory sense of other animals, notably dogs, is even more acute than that of man. One of the best examples is the ability of the bloodhound to follow a trail. On the other hand, the olfactory sense is unreliable in some respects and is easily fatigued by a particular odor so that it may become entirely insensitive to it while still sensitive to other odors.

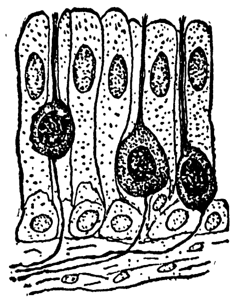


FIG. 117.—Section of olfactory epithelium. With types of cells as described on page 220. Diagrammatic. (*Wieman.*)

It has been stated in an earlier section that four primary tastes are recognized and that the flavors of foods and other substances are usually complex reactions primarily associated with the sense of smell (page 45). This can be proved by noting the absence of taste when the olfactory sense is not functioning. A great deal of work has been done in an attempt to classify the primary odors on the same basis as primary tastes. Various schemes have been proposed in which from three to nine primary odors were recognized. Recent work favors the establishment of four primary odors, thus bringing the olfactory sense into line with the other cutaneous sensations, namely, pressure, heat, cold, and pain in the skin; and sweet, sour, salt, and bitter in the chemical receptors of the tongue associated with taste. The four primary odors as now recognized are termed *fragrant* (flowery), *acid* (vinegary), *burnt* (tarry), and *caprylic* (rancid). By using the numerals from 0 to 9 to represent the complete absence and the increasing concentration of the primary odors present in a certain substance, the perfumers have been able to standardize perfumes by designating them with numbers. Thus by this system the odor of oil of wintergreen is described by the number 8442 which means that it is strongly fragrant (8*f*), with moderate amounts of the acid and burnt units (4*a*, 4*b*), and a slight amount of caprylic (2*c*). Damask rose is designated numerically as 6523, and ethyl alcohol as 5301. Experts in this field are able to get a conception of the odor of a new perfume by the number assigned.

The Sense of Hearing and Position.—The ear is a highly developed sense organ which contains receptors for two types of stimuli: those of

sound and those of position, or equilibrium. The human ear consists of three basic structural and functional units. There is, first, the visible outer ear which functions as an accessory structure for collecting the sound waves and passing them on to the middle ear. The middle ear is also an accessory structure and contains the elements adapted for sound transference from the outer ear to the inner ear. In the inner ear are additional accessory structures and the essential auditory neurons which are the receptors for the incoming sound vibrations. (Plate XIII*A*, page 229.)

The external ear consists of a cartilaginous pinna, variable in size and shape, with a central passage (auditory canal) continuing to the middle ear like the neck of a funnel. The inner end of the auditory canal is closed by a vibrating drum or tympanic membrane. The distal portion of the auditory canal connecting with the external pinna is cartilaginous, but the inner portion is bony. The canal is uniformly lined with skin containing special areas which secrete a protective wax. Entrance to the auditory canal is guarded by numerous projecting stiff hairs. The tympanic membrane, which marks the inner boundary of the external ear, is so constructed that impinging sound waves cause corresponding vibrations.

The middle ear is an irregular-shaped cavity located in the substance of the temporal bone. Laterally, that is, toward the outer ear, the cavity is terminated by the tympanic membrane. In the opposite direction, approach is made to the structures of the inner ear. Dorsally, the middle ear cavity ends in irregular air spaces in the temporal bone. Opening into the cavity is an air tube (Eustachian tube) which connects with the throat region and serves to keep the air pressure equalized on the tympanic membrane. When the Eustachian tube is partially or entirely clogged as the result of an infection, the air pressure is gradually reduced in the cavity of the middle ear by continued swallowing, and the tympanic membrane is pushed inward by the external air pressure. This condition results in lessened vibrating efficiency.

Functionally important in the middle ear are three tiny bones, the auditory ossicles, which are responsible for receiving the vibrations from the tympanic membrane and carrying them across the cavity of the middle ear to that of the inner ear. Joined to the inner surface of the tympanic membrane is the first of these bones, the malleus (hammer) which, in turn, articulates with the incus (anvil). The third member of this auditory bone-bridge is the stapes (stirrup). It articulates with the incus laterally and then continues to the tiny

so-called oval window (fenestra ovalis) which marks the beginning of the inner ear. The fenestra ovalis and another similar opening, the fenestra rotunda, lying just below, are tiny openings in the bone tissue leading from the middle ear to the inner ear. Each is completely shut off from the middle ear by a membrane. The two ends of the U-shaped stapes are attached to the fenestra ovalis membrane, which clearly indicates that the auditory vibrations are transmitted to the inner ear at this point. (Plate XIII*A*, *B*.)

The inner ear (labyrinth) is also situated in the temporal bone just beyond the middle ear cavity. It is a structure of extreme complexity in the human adult. The labyrinth consists of an outer covering of unusually hard bone tissue (bony labyrinth) molded, so to speak, to conform to the shape of the delicate membranous labyrinth that it encloses. Between the membranous and the bony labyrinths is a space filled with a fluid, the perilymph. The latter apparently serves as a medium for the transfer of vibrations received from the auditory ossicles at the oval window to the second fluid, the endolymph, which fills the interior of the membranous labyrinth. The endolymph actually bathes the sensory cells present in the membranous labyrinth and, in some way, manages to convey the qualities of the original sound waves impinging upon the eardrums. The essential functional elements of the ear are, as just indicated, within the membranous labyrinth. (Plate XIII*C*.)

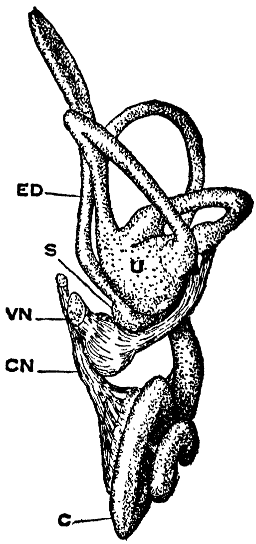


FIG. 118.—Membranous labyrinth of human embryo (30 cm.). *C*, cochlea; *S*, sacculus; *U*, utriculus with semicircular canals; *CN*, cochlear branch of auditory nerve; *VN*, vestibular branch of auditory nerve; *ED*, endolymphatic duct. (*Wieman, after Streeter.*)

The membranous labyrinth is first seen in the embryo as a tiny depression in the outer ectoderm on each side of the head region. A little later the depressed area is entirely cut off from the outer surface and forms a tiny closed vesicle. Then the latter differentiates into an upper vestibular portion (utriculus) and a lower cochlear portion (sacculus). From the utriculus, as development proceeds, three semicircular canals are formed which function in connection with equilibrium; and, from the sacculus, the coiled cochlea, in which the auditory sense is localized, gradually takes its permanent structure. Both the semicircular canals and the cochlea are innervated by separate bran-

ches of the auditory nerve that comes from the central nervous system. The interior cavities of the labyrinth are continuous and filled with the common endolymph. (Fig. 118.)

Semicircular Canals.—Considering, first, the structural arrangement of the semicircular canals that develop from and remain continuous with the utriculus, it is important to note that the canals lie in three different planes at approximately right angles to each other. Each canal may be described as a tubular horseshoe-shaped structure, both ends of which are welded to the utriculus. One end of each canal, near its union with the utriculus, is enlarged to form a circular ridge, or ampulla, in which a sensory structure (crista acustica) is located. The

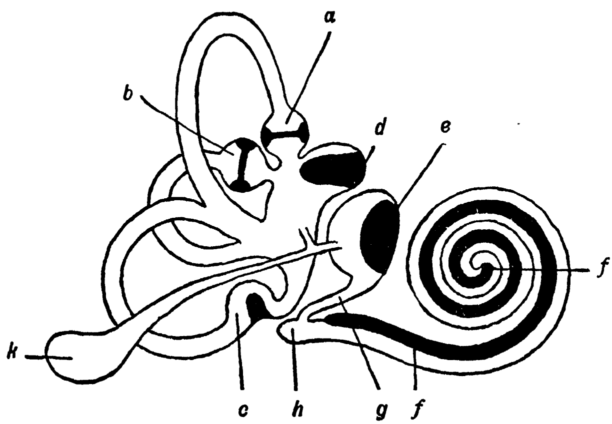


FIG. 119.—Diagram showing sensory areas (black) in the semicircular canals and cochlea of the left ear. *a, b, c,* superior, lateral, and posterior semicircular canals with ampullae; *d,* macula utriculi; *e,* macula sacculi; *f,* organ of Corti, *k,* saccus endolymphaticus. (*Maximow-Bloom, "Histology," W. B. Saunders Company. From Shaffer, after von Abner, slightly modified.*)

latter, when the ampulla is opened, is seen as an elevated ridge occupying about one-third of the canal cavity. Covering the top of the ridge and extending for a distance on each side are ciliated sensory neurons with associated supporting cells. The cilia do not project directly into the endolymph but into a covering layer of gelatinous material perforated with tiny canals, through which the endolymph reaches the cilia. Histologists have found it impossible to make satisfactory microscopic preparations of the crista of the mammalian ear, and certain details both of structure and function are still unknown.

It has long been known from experimental data that the sensory cells in the semicircular canals are influenced by changes in the body position and that, in some way, the stimuli received by the central nervous system from these stimulated sense organs are used as a basis

for the coordinated muscle control associated with the erect posture of man. Presumably the more or less continuous impulses from the sensory cells of the semicircular canals are integrated with the proprioceptive impulses in determining the necessary course of muscle action. It is assumed that variations in the endolymph pressure, corresponding to the head movements, stimulate the canal receptors, but absolute proof of this and of other suggested theories of semicircular canal functions is still lacking. The problem is further complicated by the fact that a highly developed sensory apparatus (macula acustica), essentially of the same nature as the crista of the canals but containing otoliths, is a permanent feature of the sacculus and of the utriculus. It is generally believed that the maculae also share in the equilibratory function of the ear, but again proof is lacking. (Fig. 119.)

Cochlea.—The essential auditory organ, the cochlea, as found in man and the higher vertebrates, is one of the most complex of all the organs in the body and least understood from a functional standpoint. The cochlea is not present at all in the lower vertebrates, where the ear is primarily an organ of equilibration, but it assumes increasing structural and functional importance in the higher groups. The forerunner of the cochlea is seen in the lower vertebrates as a tiny teat-like projection (lagena) of the sacculus. The mature cochlea of the human ear viewed externally is a coiled bony structure, fashioned like a snail shell with two and one-half turns around the central axis. This coiled cochlear tube has the greatest diameter proximally where it connects with the sacculus and gradually narrows down distally to a blind ending in the center of the coil. All in all, it is about 1½ in. long, around 0.1 in. in diameter, and filled with the fluid perilymph. (Fig. 119.)

Contained in the outer bony cochlea is an inner membranous cochlear canal (scala media), which contains the endolymph and the sensory cells grouped in the spiral organ of Corti. This cochlear canal is considerably smaller than the osseous cochlea that encloses it, but of course it follows the snail-like curvature of the latter. If, now, a transverse section of the cochlea is examined, it will be seen that the enclosed cochlear canal is not circular but roughly three-sided, or trihedral, in outline. The apex of the trihedral figure projects about two-thirds of the distance across the cavity of the enclosing bony cochlea. From the wall of the latter, however, a bony projecting shelf (spiral lamina) extends out the remaining distance so that a transverse section of the cochlear canal shows a complete partition that divides the bony cochlea into an upper portion (scala vestibuli) and a lower portion (scala tympani). The latter is considerably larger than the scala vestibuli

because the membranous cochlear canal (scala media), noted above, lies entirely above the partition and occupies about one-half the space that would otherwise be open to the scala vestibuli. (Fig. 120.)

We have just seen that one side of the membranous cochlear canal is continuous at the apex with a projecting shelf or spiral lamina of the bony cochlea; thus a division is formed between the scala media and scala tympani. The division between scala media and scala vestibuli is a thin undifferentiated membrane which constitutes a second side of the cochlear canal. The base, or third side, of the latter is in contact with the inner wall of the cochlea. The arrangement of

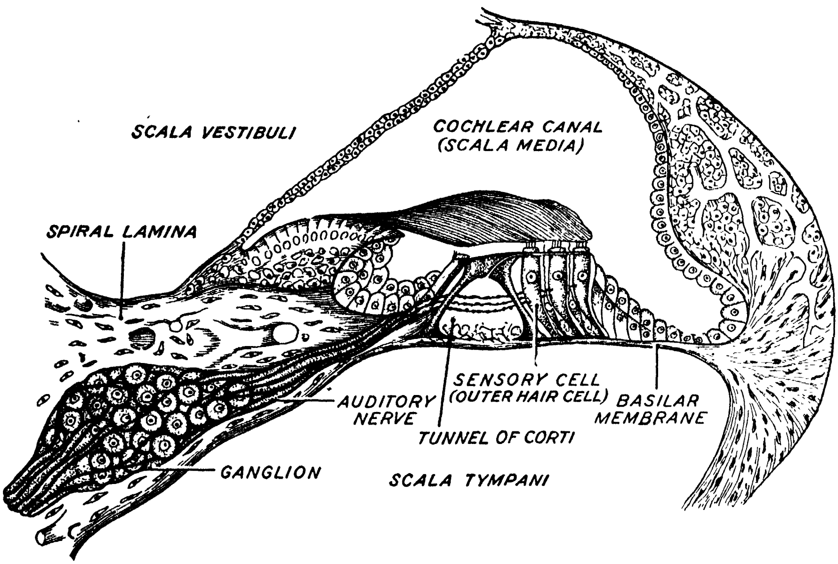


FIG. 120.—Diagrammatic section through the cochlea to show a portion of the organ of Corti, as described on page 227 *Cf.* Plate XIII *D.* (*Buchanan,* "*Elements of Biology,*" *Harper & Brothers.*)

chambers in a transverse section of the cochlear canal may be visualized by taking a pair of dividers, separating the points 3 or 4 in., and then placing them flat on the desk, with the hinge at the left and the separated points at the right. The hinge at the left represents the apex of the cochlear canal at the point where it joins the spiral lamina. Now place the back edge of a book in contact with the points. The three-sided area formed by the arms of the dividers and the edge of the book represents the cavity of the cochlear canal, or scala media, which is filled with endolymph. The upper arm of the dividers separates the scala media from the scala vestibuli, and the lower arm does the same for the scala tympani. It also bears on its upper surface,

that is, within the scala media, the highly differentiated auditory elements comprising the organ of Corti.

Organ of Corti.—Many pages could be devoted to a description of the known structural and functional features of the organ of Corti. Even so, at the present time, it would not be possible to describe it completely, because certain of the details have never been successfully worked out. For the inherent delicate nature of the tissues associated with the organ of Corti, together with its very inaccessible position, embedded as it is in the recesses of the temporal bone and enclosed by the bony tissues of the cochlea and also by the membranous wall of the cochlear canal, have so far made it impossible to fathom all of its structural complexities. Its general plan, however, is well known. In the first place, it must be remembered that both the cochlea and the enclosed cochlear canal are coiled, spiral structures, and, therefore, the organ of Corti, lying within the cochlear canal, has essentially the same length and spiral pattern of the enclosing structures. In a transverse section of the cochlea, the organ of Corti appears as a ridge on the inner surface of the wall that separates the scala media from the scala tympani, as just noted in the preceding paragraph. The tectorial membrane, projecting from the spiral lamina, is in close contact with a part of the upper surface of the cochlear apparatus. The portion of the wall bearing the complex sensory mechanism of the organ of Corti is known as the *basilar membrane.* The latter has an unusual and complex arrangement of radiating connective tissues that permits vibration. Some authorities have held that the basilar membrane is the primary functional unit of the ear. (Fig. 120.)

Five main types of sensory cell are supported by the basilar membrane. These are the inner and outer tunnel cells, the inner and outer hair cells, and the supporting cells. The tunnel cells are peculiar in shape, each with a wide base in contact with the basilar membrane and a narrow elongated body. The bases of the inner tunnel cells are separated some distance from those of the outer tunnel cells, but distally they bend toward each other so that the distal ends of inner and outer tunnel cells are in contact at the upper surface of the organ of Corti. The roughly triangular space thus formed between the cells is the tunnel of Corti.

The arrangement, just described, may be visualized by placing the right hand palm down on the table. Now slightly flex the thumb and fingers, thus raising the palm from the table so that the hand will be supported by the tips of the thumb and fingers. In this position, the surface of the table under the hand will represent the basilar membrane; the forefinger, one of the inner tunnel cells; the thumb, one

of the outer tunnel cells; and the space between forefinger and thumb, the tunnel of Corti. It is estimated that there are about 5,600 of the inner tunnel cells and 3,850 of the outer tunnel cells, each type arranged side by side in a single row and the two rows separated proximally by the width of the tunnel. The visualization of a spiral-shaped hand with this number of fingers and thumbs may possibly convey the idea.

In close association with the inner and outer tunnel cells are the inner and outer hair cells. These are the specific sensory cells through which connection is made with the nervous system. The hair cells are small, fairly typical in shape, and are arranged in regular rows on each side of the tunnel cells. They are not in contact with the basilar membrane but hang down suspended by one end, as it were, from the upper surface of the sensory epithelium. Projecting into the endolymph from the attached upper end of each of these cells are some 40 to 60 sensory hairs. It is estimated that there are around 20,000 of the hair cells. Referring once more to the analogy with the hand as stated in the preceding paragraph, we may let the knuckles represent the line of fusion of the inner and outer tunnel cells, and the back of the hand the upper surface of the sensory epithelium, bathed by the endolymph. Thus the ends of the hair cells, together with numerous associated supporting cells, form a cellular mosaic marking the upper boundary of the organ of Corti, and the hairs on the back of the hand represent the position of the sensory hairs projecting from the hair cells into the endolymph. To complete the analogy, the hand, position as given, may be visualized as immersed in water. In this case, the portion of the container on which the hand rests will represent the basilar membrane, and the water will represent the endolymph that fills the tunnel of Corti, covers the upper surface of the hair cells with the sensory hairs, and completely fills the cochlear canal. (Fig. 120.)

Ear Function.—Various theories have been proposed to account for the ability of the human ear to detect and analyze the wide variety of sounds that reach it. There is no question about certain features concerned with the transmission of sound waves through the external and middle ear to the perilymph and endolymph of the inner ear, but no adequate explanation has been made of the incredible ability of the organ of Corti to distinguish among the tremendous variety of sounds in such a way that corresponding distinctive nerve impulses can be sent to the brain for interpretation. Briefly, the organ of Corti transforms sound waves into a tremendous variety of distinctive nerve impulses which can be interpreted by the brain. When one considers that the human ear is able to distinguish sounds that vary in strength or loudness, in pitch, and in quality, the problem of inner ear function becomes highly complicated.

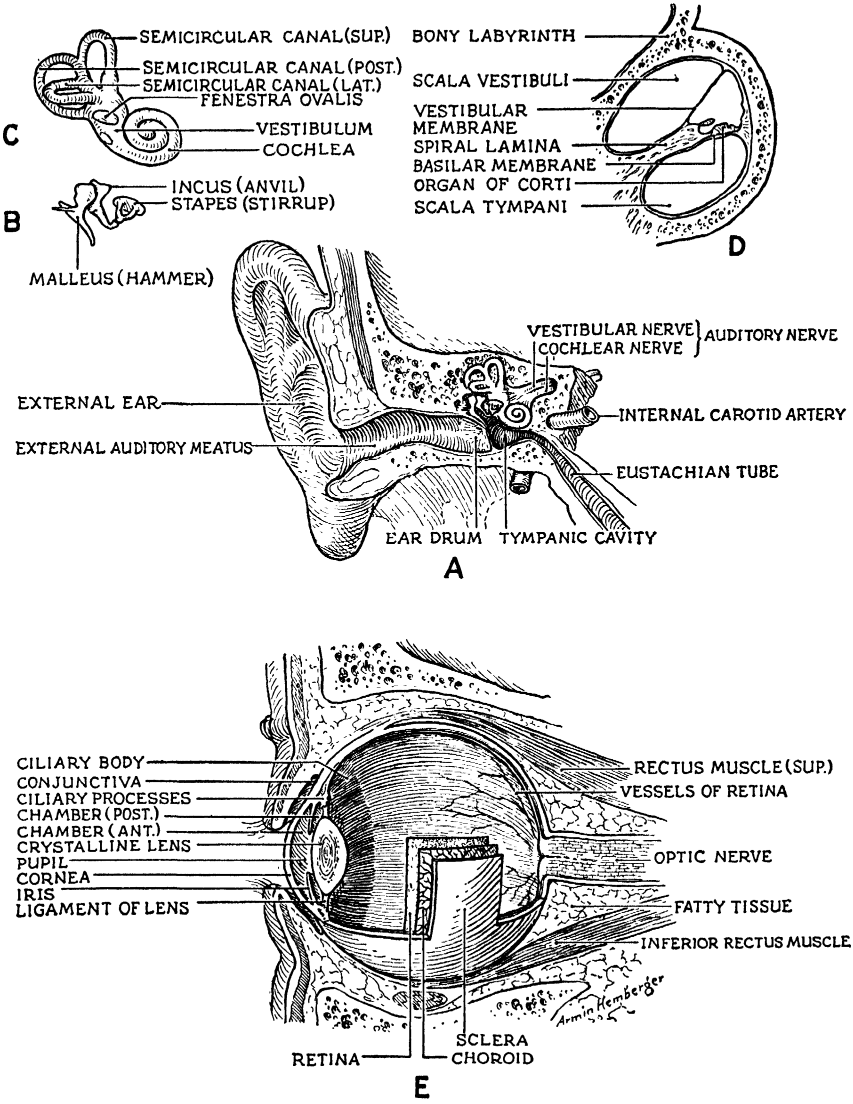


PLATE XIII.—Sense organs of man. *A*, section showing the general structure of the ear; *B*, auditory ossicles; *C*, internal ear; *D*, section showing internal structure of the cochlea; *E*, vertical section through the eye to show internal structure. Diagrammatic.

Detectable variations in pitch alone range from very low-pitched sounds with about 20 vibrations per second up to very high notes with some 40,000 vibrations, and all of these tones may vary in intensity and be associated with overtones that give a distinctive quality. It has been suggested that the basilar membrane acts as a vibrating membrane in which certain regions are responsive to particular types of incoming waves. Other authorities suggest that it acts like the vibrating disc in a telephone receiver which vibrates as a unit for every type of sound wave. It was long held that the peculiar tunnel cells (rods of Corti), described above, acted essentially as tuning forks, sympathetic to certain types of vibration, but there are far too few of them to account for the tremendous variety of sounds received by the ear. All in all the problems associated with our highly developed sense of hearing are far from solved. Of the end result, there can be no doubt; of the methods used in the organ of Corti to obtain the results, there is uncertainty.

The Sense of Sight.—The eyes are special sense organs devoted exclusively to the function of sight, or vision. The eye is essentially an optical instrument of the camera type, so arranged that light can be focused upon a sensory tissue, the retina, which is capable of determining the intensity and the wave lengths of the incoming light rays.

Eyeball.—The main structural unit is the eyeball, which, in the human eye, is almost spherical in shape and approximately 1 in. in diameter (Fig. 121). Well-developed accessory structures are necessary for the functioning of the essential sensory neurons in the retina, some of which lie outside the eyeball and some lie inside. The external accessory structures include the attached muscles which move the eyeball; the eyelids, with a special epithelial lining, the conjunctiva, which also covers the exposed anterior surface of the eyeball; and the glandular lachrymal apparatus which secretes a cleansing and lubricating fluid. The internal accessory structures include the iris diaphragm which regulates the amount of light admitted through the anterior opening, or pupil; the lens, directly back of the pupil, which is responsible for focusing the light rays on the retina; the important and highly specialized muscle tissue which is associated with the necessary structural changes in the iris and lens; and, finally, the transparent, semifluid humors which fill the interior cavities of the eyeball. (Plate XIII*E*.)

The eyeball is enclosed externally by a strong connective tissue sheath, or sclera (tunica fibrosa), which forms a continuous covering, except for a small circular area in the back of the eye where it is pierced by the optic nerve running from the retina to the brain.

The tissue of the sclera is opaque, except for a small area directly in the front of the eye where it forms the transparent, window-like cornea through which the light rays pass on their way to the lens. Lying within the sclera is the choroid layer. It is very vascular, deeply pigmented and, in the front of the eye, forms the colored, contractile iris with a circular opening, the pupil, in the center. The iris contains muscular elements and, in its functional aspect, may be compared to the adjustable iris diaphragm of the camera which can be regulated as desired according to the intensity of the light. When the light is dim, the radiating muscles in the iris contract, thus enlarging the pupillary opening through which light passes to the interior of the eye. In a bright light, the circular muscles of the iris involuntarily contract, and this results in a constriction of the pupil so that a reduced amount of light is admitted to the sensitive eye tissues. The third and innermost layer of the eye is the retina, characterized by the presence of unique functional visual elements (rods and cones) adapted for receiving the photic stimuli and passing the resulting impulses into the nervous system for transmission to the brain via the optic nerve. The retina lines the posterior portion of the eyeball but does not form a complete anterior layer as do the sclera and choroid.

The eye lies in a deep-seated skull cavity, the socket, or orbit, well-protected by the surrounding bony tissues. The exposed anterior portion of the eyeball is covered by a special type of epithelium, the conjunctiva, arranged in two layers; the inner layer, thin and transparent, covers the exposed portion of the eye and is directly attached to the cornea and near-by regions of the sclera. Peripherally, this layer merges into the outer conjunctival layer which forms the lining of both eyelids. At the edges of the lids, in the region of the eyelashes, the conjunctiva becomes continuous with the skin tissues. The eyelids themselves contain muscle elements, both smooth and striated, together with connective tissues and numerous glands. The latter open on the edges of the lids in the region where the conjunctiva and skin merge. (Plate XIII*E*.)

Lachrymal Glands.—The almost continuous movements of the eyeball and the eyelids during the day require that the conjunctival surfaces be well supplied with a moistening, lubricating, and cleansing medium. To furnish this medium is the function of the lachrymal glands which pour their secretion through the lachrymal ducts; the latter open through the conjunctiva near the outer edge of the upper eyelid. The lachrymal gland of each eye is roughly almond-shaped and is lodged between the eyeball and the bony socket, above and well to the outer edge. The lachrymal secretion flows downward over the exposed eye surfaces and is continuously drained off through the

openings of the tear ducts, situated close to the inner junction of the upper and lower lids. The two ducts of each eye, one from the upper lid and one from the lower, unite to form the lachrymal sac which opens into the nasal cavity. An excess of the lachrymal secretion, as in laughing or crying, causes the tears to overflow and roll down the cheeks.

Voluntary movements of the eyeball are brought about by three pairs of muscles which are inserted in the sclera and anchored to the surrounding bony tissues. These paired muscles include (1) the superior and inferior recti, attached above and below, respectively, by means of which the eye is rolled up and down; (2) the anterior and

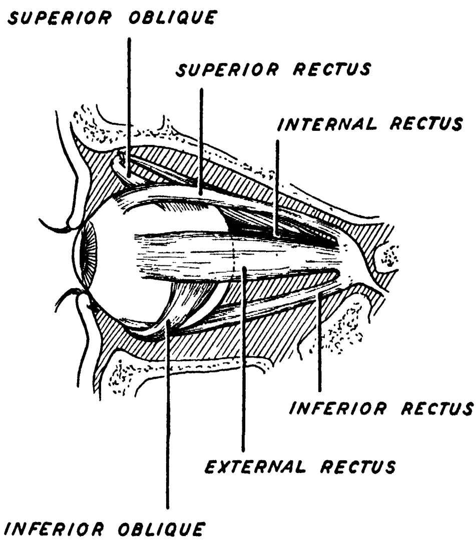


FIG. 121.—Dissection to show the eyeball and the arrangement of the muscles responsible for eye movements. (*Buchanan, "Elements of Biology," Harper & Brothers.*)

posterior recti, attached medially and laterally, through which the eye is revolved to the right or left; (3) the superior and inferior oblique, attached above and below in such a fashion that oblique movements of the eyeball are possible. A pair of strong median and lateral ligaments attached to the sclera near the junctions of the lids extends into the bony tissue of the nasal region and laterally into the bone at the outer edge of the orbit and limits the eye movements and keeps the eyeball securely lodged in its orbit. (Fig. 121.)

With the general external structure of the eye in mind, attention may be directed to its important internal structural and functional features. Observations on a mammalian eye, which has been cut in half in a vertical plane, shows a division into a comparatively large

vitreous chamber, lying posteriorly, and a small anterior chamber. The anterior chamber extends from the cornea posteriorly to the iris. Between the iris and the anterior surface of the lens, an even smaller chamber communicates with the anterior chamber through the opening of the pupil. These two chambers contain the aqueous humor, a transparent watery fluid secreted by certain of the surrounding tissues. The aqueous humor is continuously replaced, as necessary, to restore that lost by the drainage. Posterior to the lens is the large vitreous chamber, noted above, which is mostly lined by the retina. It is filled with the vitreous humor, a permanent, transparent, noncellular material of gelatinous consistency. (Plate XIII*E*.)

Accomodation.—The incoming light rays pass first through the pupillary opening and then through the lens which is directly behind.

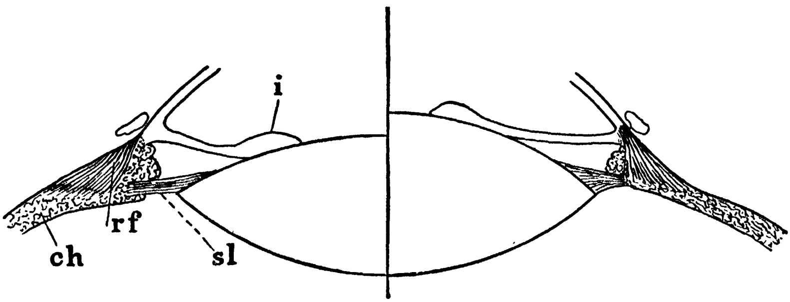


Fig. 122.—Illustrating the mechanism of accommodation, as described on page 233. To the right, thickened lens, accommodation for a near object; to the left, thin lens, accommodation for a distant object. *ch*, ciliary process; *i*, iris; *sl*, suspensory ligament; *rf*, ciliary muscle. (*Martin, "Human Body," Henry Holt & Company, Inc.*)

The latter is constructed of highly modified epithelial cells, each drawn out into a transparent ribbon-like stucture, and all closely joined and held in position by an intercellular cement substance. The lens is a biconvex, crystalline body so constructed that it can change its shape —the function of accommodation—which is necessary in order to focus the light waves from near and distant objects on the retina. The lens is enclosed by a substantial membrane, or lens capsule, closely applied to the outer lens epithelium. The lens capsule is continuous, all the way around, with a tendon-like ligament attached to the ciliary muscles. The latter form a ridge extending toward the lens from the choroid layer at the base of the iris. Also these muscles are so arranged that, when they contract, tension is lessened on the ligament attached to the lens capsule, and the highly elastic lens is thereby permitted to assume a more spherical shape. The increased curvature makes the lens stronger, that is, capable of bending the light rays from near objects, as in reading, so as to bring them to a focus on the

retina. When the ciliary muscles relax, the tension on the lens capsule is increased, and the lens is flattened and thus adapted for focusing the images of distant objects on the retina. And so the lens is able to accommodate for near and distant vision by altering the curvature. The same result is attained in a camera by adjusting the distance between the lens and the sensitive film surface. (Fig. 122.)

In a considerable number of individuals, the accommodation of the eye is not perfect. The lenses may be consistently too strong and bring the objects to a focus in front of the retina. This is nearsightedness, and the individual compensates by moving the object nearer to the eye. Farsightedness is the opposite condition in which the lenses are not strong enough, and consequently the rays are focused back of the retina. The farsighted individual endeavors to compensate by holding the book or other object farther from his eyes. The faulty accommodation is not always due to an abnormal lens; it may be due to the fact that the distance between the lens and the retina is abnormally long or short. A third error in refraction, astigmatism, is due to irregular curvature of the lens. The oculist is able to measure the optical condition of the eye and to prescribe artificial lenses that will correct the deficiencies of the regular lenses. (Fig. 123.)

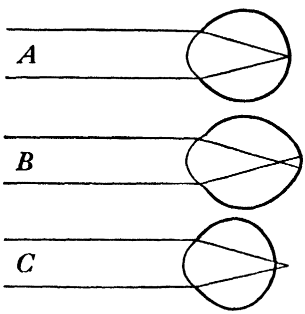


FIG. 123.—Illustrating the paths of parallel light rays in a normal eye (*A*), short-sighted eye (*B*), far-sighted eye (*C*). (*Martin, "Human Body," Henry Holt & Company, Inc.*)

Retina.—The retina is one of the most complex tissues in the entire body, and therefore it may be well to begin our description with its development in the embryo. Such a study will show that the retina is the first structure of the eye to develop and, also, that it is formed from the ectoderm of the brain region. Later, the developing retina is doubly enclosed by the choroid and the sclerotic layers, both of which are mesodermal in origin. The retina grows out laterally from the newly formed neural tube, in the region of the developing forebrain, until it comes into contact with the epithelial cells covering the body surface. The epithelial cells, which are thus brought into contact with a developing retina, gradually become transformed into the lens.

At first, the retinal outgrowth is seen as a hollow, club-shaped group of cells, but the shape of the distal end is soon changed by a secondary invagination and develops into a double-walled, cup-shaped structure which becomes the retina proper. This develop-

mental process can be visualized by holding a spherical toy balloon, lightly inflated, in the palm of one hand and pressing against it with the closed fist of the other hand. In this position, the fist represents the crystalline lens at the lateral surface of the head. The balloon, now double-walled and partially enclosing the lens, represents the retina, which consists essentially of an inner sensory layer (represented by the balloon wall surrounding the fist) and an outer pigmental layer (represented by the outer balloon wall in contact with

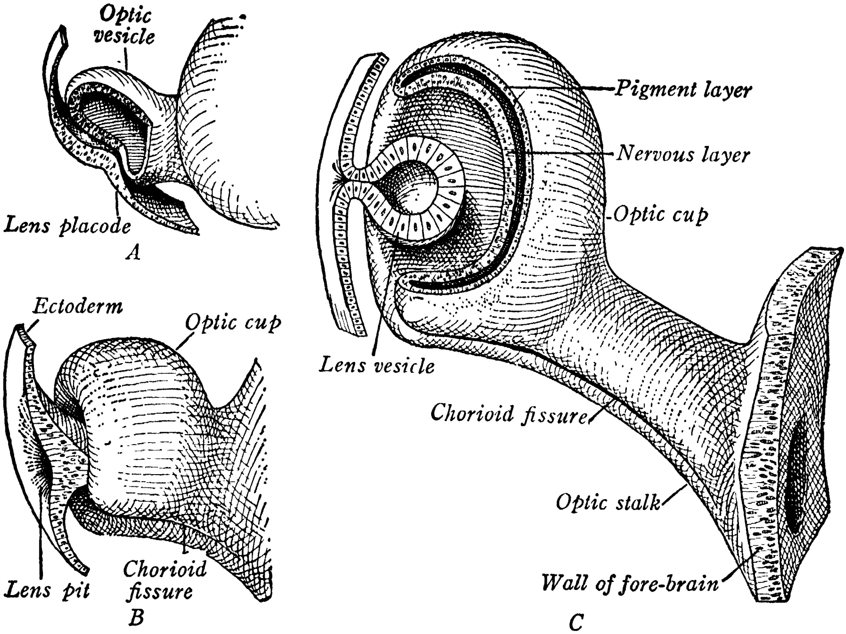


FIG. 124.—Illustrating the development of the retina in the human eye as an outgrowth from the forebrain, described on page 234. *A*, from 4.5 mm. embryo; *B*, from 5.5 mm. embryo; *C*, from 7.5 mm. embryo. (*Arey, "Developmental Anatomy," W. B. Saunders Company.*)

the palm of the other hand), which is soon to be covered by the choroid layer. The optic nerve, which connects the visual cells of the retina with the sensory area in the brain, is gradually fashioned out of the proximal portion of the original outgrowth from the forebrain. (Fig. 124.)

Our next concern is with the mature retina which gradually assumes an extraordinary complexity of the constituent tissues as noted above. The general pattern of the retinal tissues follows to a considerable extent the basic pattern of the brain tissue from which it developed. The microscopic study of retinal tissue is most profitable

when a vertical section is examined, taken at right angles to the upper surface. Such a preparation shows that the retina consists of no less than 10 distinct layers. The outermost of these is the pigmented, nonsensory layer, which is in contact and fused with the choroid layer. The pigmented layer is relatively thin and consists primarily of pigmented epithelial cells. All of the remaining nine layers of retina develop from the original inner layer of the retinal outgrowth and form a relatively thick sensory tissue (about 0.0125 in.) built up of

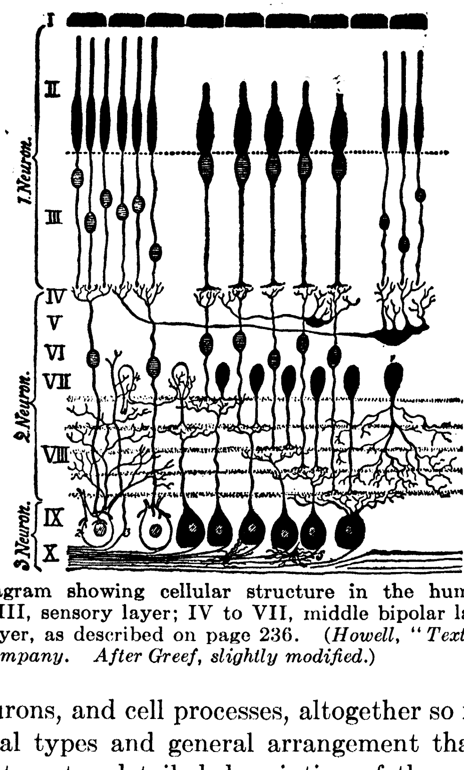


FIG. 125.—Diagram showing cellular structure in the human retina. Highly magnified. II to III, sensory layer; IV to VII, middle bipolar layer; and VII to X, inner ganglionic layer, as described on page 236. (*Howell, "Textbook of Physiology," W. B. Saunders Company. After Greef, slightly modified.*)

visual cells, neurons, and cell processes, altogether so intricate in their varied structural types and general arrangement that it will not be profitable to attempt a detailed description of the separate layers in the present discussion. (Fig. 125.)

The basic structural condition may perhaps be understood by recognizing three divisions in the functional retina, namely, (1) the outer photoreceptor, (2) the middle bipolar, and (3) the inner ganglionic. In the photoreceptor division, which lies in contact with the outer pigmented layer, are the specialized visual elements. These cellular elements are found to consist of two types: the rods and the cones, both of which are elongated cells with unique structural and functional features. They lie perpendicular to the curved surface of the eyeball,

regularly arranged, with the distal ends in contact with the pigmented layer. Processes from the pigmented cells project inward for a considerable distance between the visual cells and thus partially separate them. The rods, as the name indicates, are slender, tubular structures. They contain a complex substance, visual purple, which is known to be chemically changed by light waves. The inner or proximal end of each of these cells tapers down to a very fine protoplasmic filament, or rod fiber, in which the nucleus is located. The rod fibers extend toward the middle of the retina where they connect with processes from the bipolar neurons. The cones lack the visual purple but are essentially similar to the rods in their structure, except that the body of the cell is heavier, shorter, more club-shaped, and the nucleus-containing cone fiber is considerably thicker. There is no apparent reason why this should be so, and, as a matter of fact, certain types of cones are thin, elongated bodies which are similar in appearance to the rods. (Fig. 126.)

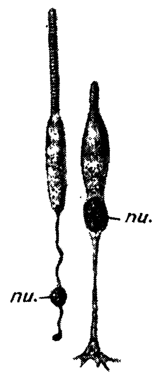


FIG. 126.—Receptor cells from human retina. Rod cell, left; cone, right. Highly magnified. *nu.*, nucleus in rod and cone fiber. (*Weber-Valentine.*)

The middle region of the retina contains the so-called *bipolar cells.* These are elongated nerve cells adapted for receiving the impulses from the terminal fibers of the rods and cones. The impulses are received from the visual cells at the fiber end by union, or synapse, then transferred to the neurons of the ganglionic division of the retina. The cell processes of the ganglionic neurons extend to the inner surface of the retina and converge in great numbers to form the large optic nerve. Thus it is seen that the light rays entering from the front of the eye penetrate the ganglionic and bipolar divisions of the retina without stimulating any of the constituent cells, before finally reaching the distal ends of the rods and cones that are sensitive to them. And the resulting impulses are carried in the reverse direction through the neurons to reach the elements of the optic nerve over which they are carried to the brain for interpretation. (Fig. 125.)

There is considerable variation in the sensory quality of the retina, depending upon the distribution of the rods and cones. Toward the front of the eye, the numbers of rods and cones are greatly reduced, and, in the extreme periphery of the retina, they are entirely absent. A definite blind spot is found in the comparatively small central area where the optic nerve terminates at the inner surface of the retina. The area of most acute vision in the retina is found in the tiny fovea

centralis, about $\frac{1}{8}$ in. in diameter, which lies directly back of the lens in the so-called optical axis of the eye. In the fovea, the thickness of the retina is greatly reduced by the complete omission of the bipolar and ganglionic layers so that the visual cells are almost directly exposed to the incoming light rays. Furthermore, only cones are present in this region. An object to be seen clearly must be in the line of direct vision, or in the optical axis, so that the image will be focused on the fovea, as just noted. Involuntarily, the eyes are continually being moved so as to bring an object in the field of acute vision. Light rays falling upon the more peripheral regions of the retina are seen only dimly. This is due primarily to the reduced numbers of visual cells, which correspondingly decrease the resolving power of this region.

Light Rays.—Certain important facts relative to the physical characteristics of the visible light rays should be noted. We may regard light as being produced by minute but very rapid vibrations which have their source in an object heated to a high temperature. Thus the metal filament in an electric light bulb, when heated to a sufficiently high temperature by the passage of an electric current, gives off visible light waves. In such a case, the potential energy of the coal or other fuel burned in the powerhouse or that of water power is converted into energy-bearing light waves, and the latter stimulate the visual elements in the eye. In nature, however, the source of the light energy is, as we well know, the sun. As a matter of fact, the sun is the source of the electric light energy, for the energy both in the fuel burned or the water used in order to generate the electric current came originally from the sun.

The physicist, by means of the spectroscope, can analyze light and thus determine its nature. When, for example, sunlight is allowed to pass through the glass prism of a spectroscope, it emerges as a multicolored spectrum with visible bands of red, orange, yellow, green, blue, and violet, the so-called spectral colors. These colors are commonly seen in the rainbow, which results from the dispersal of the rays of sunlight by passing through raindrops. The latter act as does the prism in the spectroscope of the physicist. Thus it is clear that white light is a mixture of different colors. Furthermore, it is known that the different colors are due to variations in the length of the light waves. In the visible spectrum, the latter range from an extreme length of 760 millionths of a millimeter in the case of red light to 390 millionths at the violet end of the spectrum. Other energy-containing rays lie above and below the visible spectrum. Thus, above the red rays are longer, invisible infrared rays; below the violet are the ultraviolet, both of which, though ineffective in stimulating

the visual cells of the retina of the eye, can be detected by the proper physical instruments. (Fig. 229.)

From the foregoing, it is evident that the retina of the eye is essentially a tissue capable of responding to light rays of certain lengths. But how the rods and cones do this is entirely beyond our present knowledge. It is clear that the peculiar compound present in the rods, visual purple, is in some important way concerned in this reaction, but it is also certain that this substance is not the primary element of vision, for, in the fovea, the region of most acute vision, only cones are present, and they lack the visual purple. Also it is known that visual purple is entirely lacking in the retinal tissues of some animals, such as the pigeon and bat, which, as flying animals, undoubtedly have acute vision. About all that can be said with certainty is that the essential visual elements are located in the protoplasm of the rods and cones. (Fig. 126.)

Color Vision.—It has been noted above that white light represents a mixture of various colors of the spectrum, but we also find that various combinations of two colors will give the same visual sensation as the mixture of all the colors. These white-producing pairs of colors are known as *complementary colors*, examples of which are seen in certain shades of red and blue, yellow and blue, etc. Since two complementary colors will produce white when added together, it follows that, when one of the complementary colors is removed, the visual color sensation changes from white to that of the other member of the pair. This can be well shown in the phenomenon involving retinal fatigue. Thus if one looks intently for about one-half minute at a brilliant red color and then quickly transfers his vision to a white surface, a brilliantly colored area will be seen on the white surface, but the latter will be bluish-green in color, which is the complement of red. This is due to the fact that the retinal elements responding to the red color have become fatigued and do not respond, thus giving white minus the red, which is the green complementary. Furthermore, the physicist recognizes three fundamental colors (red, green, and blue) by the proper mixture of which white and all other colors can be produced. This fact has long been linked up with important theories of color vision which assume that the visual cells respond to the three primary colors and that the multiplicity of color sensations is due to variations in the strength of the stimuli coming from the primary colors.

PERIPHERAL NERVOUS SYSTEM

Elements of the nervous system necessarily innervate every tissue of the body. The previous study of the sensory tissues has shown

that the invasion of the sense organs by the peripheral nerves is for the purpose of receiving impulses, developed in accordance with the external and internal environmental stimuli and transmitting the impulses to the central nervous system for interpretation. The innervation of the effector tissues, including the muscles and glands, is to make possible the coordinated control of their activities by the central nervous system. Thus the essential function of the peripheral nerves is the conduction of nerve impulses to and from the master tissues of the central nervous system. In order to do this, the highly differentiated animal organism possesses an extraordinarily complex system of nerves, containing many individual nerve fibers, from the early developmental stages. It has long been recognized that nerves typically contain two types of nerve fibers: the sensory, or afferent, fibers over which impulses pass into the central nervous system; and the motor, or efferent, fibers over which impulses travel peripherally from the central nervous system to the outlying effectors. This condition clearly indicates that the individual nerve fiber is a one-way track for nerve impulses. (Figs. 127, 133.)

Neuron Concept.—But the nerve fibers are not to be regarded as the basic structural and functional units of the peripheral system, for histologists studying the microscopic anatomy of nerve tissue were able, more than fifty years ago, to establish the important fact that a nerve fiber is simply a greatly elongated protoplasmic process of a neuron. This so-called neuron concept means, in essence, that the nervous system, like the other systems of the body, is composed of cells, the neurons. The neurons, as a group, are characterized by a very high degree of complexity and diversity, both structurally and functionally, marked instances of which will be seen from the later description. One unifying structural feature, however, with which we are particularly concerned in our present discussion of the peripheral system is the fact that the cell bodies of the neurons are extended to form one or, usually, more projections for the conduction of impulses; these projections are the nerve fibers. (Plate XII*D*, *E*.)

Furthermore, the neurons are not indiscriminately scattered along the peripheral nerve fibers as they ramify throughout the body tissues but are concentrated in the central nervous system or in the near-by nerve centers, the ganglia. This means, of course, that the cell processes or nerve fibers of some of these centrally situated neurons must be several feet in length, as, for example, to take an extreme case, the fibers that have their origin in the neurons in the spinal cord of the central nervous system and extend to the tips of the fingers or toes. It must be remembered, however, that the nerve fibers that originally

connected the central nervous system and the peripheral parts of the body in the very early embryo were not very long and that a gradual increase in length occurred as the embryo increased in size. Finally, it has already been indicated that a nerve fiber carries impulses in one direction only. Since the nerve fibers are cell processes, this means that there are two types of the latter: the dendrites, which carry impulses centripetally, that is, toward the cell body; and the axons, which carry impulses peripherally, that is, away from the cell body. Microscopic study has not revealed any structural differences between the axon fibers and dendrite fibers.

Nerves and Nerve Fibers.—The functional conducting elements, or nerves, are seen as glistening white cords extending everywhere throughout the body structures. Some of the nerves are tiny filaments, microscopic in size; others, as in the nerve trunks of the leg and arm, may be comparable in diameter with that of the little finger. Since all of these nerves have their origin in the brain or spinal cord of the central nervous system and near-by ganglia, they tend to increase in size as they approach the central nervous system and to divide into smaller and smaller units peripherally in accordance with the fibers given off, or received en route to innervate various regions. Care must be taken to distinguish between the *nerve* and the *nerve fiber*. The latter, as noted, is a cell process, sometimes greatly elongated but always microscopic in diameter, whereas the nerve is an aggregation of a great many tiny individual nerve fibers, insulated from each other and compactly bound together by connective tissue elements. We have already seen an example of this type of tissue construction in the building of a large muscle from microscopic muscle fibrillae (page 177). And the telephone technicians make use of the same method in building the large, lead-covered telephone cables which may contain thousands of individual copper wires, each insulated by a special covering from all the others. The variation in the size of the nerves is due primarily to the number of associated fibers. (Plate XII*A*.)

When a transverse section of a typical nerve is examined microscopically, it will be found that it is completely covered by a connective tissue sheath, the epineurium. Inside the sheath, considerable numbers of the tiny nerve fibers are grouped in bundles, and each of the latter is surrounded by the perineurium which is a continuation of the connective tissue elements of the epineurium. Further study shows that the individual fibers are separated from each other and more or less surrounded by a still further continuation of the connective tissues to form the endoneurium. In a fresh nerve, it is possible to separate the individual nerve fibers and note their plan of construction.

It is found under such conditions that a delicate sheath, the neurilemma, surrounds each individual fiber and is in contact with the endoneurium. Lying under the neurilemma is a comparatively thick layer of a fatty substance, the myelin sheath. The latter is interrupted at rather regular intervals along the nerve fiber, and the neurilemma at these points (nodes of Ranvier) is in contact with the tiny central process of a neuron—either axon or dendrite. Each axon (or dendrite) is thus separated from all the other axons of a nerve by the myelin sheath, the neurilemma, and by the connective tissue elements indicated above. The axon and dendrite differ functionally, as noted above, but structurally are not distinguishable. As a matter of fact, the axons and dendrites are not the ultimate conducting elements of a nerve fiber. This function is believed to be localized in cytoplasmic fibrils (neurofibrils) that apparently originate in the body of the neurons, near the nucleus, and extend peripherally into the axons and dendrites. In certain types of nerve fiber, the myelin sheath is lacking. Such nerves are known as the *nonmyelinated nerves* and are characteristic of the autonomic system, as distinguished from the myelinated types of spinal nerves just described. (Fig. 131.)

Cranial and Spinal Nerves.—From the extreme anterior end of the brain to the posterior tip of the spinal cord, a total of 43 pairs of cranial and spinal nerves leave the central nervous system and extend to the outlying tissues; 12 pairs of these are cranial; and 31 pairs are spinal nerves. The majority of the cranial nerves[1] have departed quite widely from the typical condition of the peripheral nerves, which is to be seen in the spinal nerves. Thus the spinal nerves are given off from the spinal cord at regular intervals; that is, they are segmentally arranged. Furthermore, each spinal nerve arises in the spinal cord by a dorsal (posterior) root and a ventral (anterior) root. A short distance from the cord, the nerve fibers of the anterior and posterior roots unite and are bound together by the common connective tissue coverings, thus forming a single large nerve composed, therefore, of both dorsal and ventral fibers. (Plate XIII*A*; Plate XIV*D*, page 248.)

Early experimental work on the spinal nerves established beyond all doubt the fact that there is a functional differentiation between the posterior and anterior fibers. The posterior fibers are afferent sensory fibers, which bring the impulses to the central nervous system from the peripheral sense organs; the anterior fibers are efferent motor fibers, which transmit the impulses from the central nervous system to the peripheral effectors (muscles and glands). And so it is evident that each spinal nerve contains both sensory and motor fibers. This

[1] Consult Appendix: Cranial Nerves.

mixed type of nerve is not always found in the cranial nerves, for some of them, as will be seen from the description below, contain either sensory fibers or motor fibers but not both (page 519). The later description of the central nervous system will give opportunity for consideration of the associations between the spinal nerves and spinal cord.

The determination of the fact that the spinal nerves contain both sensory and motor fibers led to the establishment of the conception of the reflex arc which involves a peripheral sense organ (receptor), an afferent sensory nerve fiber, the central nervous system (adjustor), an efferent motor nerve fiber, and the peripheral effector, usually muscle tissue. Thus, when the tip of the finger inadvertently touches a hot surface, it is immediately jerked away by a reflex action which involves no conscious action. It is clear in a reflex action that the sensory cells in the skin covering the finger tip are first affected. The resulting impulse is transmitted to the central nervous system over the afferent fibers of the sensory root. The central nervous system acts as an integrating mechanism (adjustor), a function that involves both the interpretation of the incoming sensory impulses and the relaying of the outgoing impulses over the efferent fibers of the proper motor roots, the ones that innervate the arm muscles. The contraction of the latter completes the drama. (Fig. 127.)

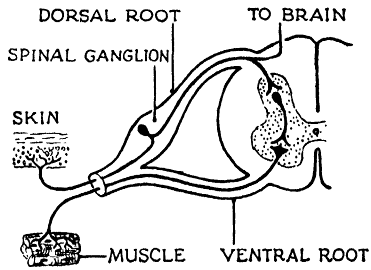


FIG. 127.—Diagram showing section through the left side of the spinal cord with the dorsal afferent root and the motor efferent root of a spinal nerve as described on page 242.

The Autonomic Nervous System

The autonomic nervous system is essentially a part of the peripheral nervous system, but the distribution of the constituent nerves is largely limited to the important visceral organs present in the thoracic and abdominal cavities, and the impulses that pass over the autonomic nerves from the central nervous system are beyond our conscious control. It is sometimes referred to as the *involuntary nervous system* because of this condition. Since the autonomic system apparently exercises a complete involuntary control over the most important organs in the body, it is usually ranked as one of the four major divisions of the complete nervous system. Basically, however, it appears clear that it is not really a controlling unit but a conducting unit which receives efferent motor impulses from the central nervous system and

conveys them over a network of the utmost intricacy to the proper effectors—the involuntary muscle elements in the visceral organs. There appears to be no evidence that the impulses that exercise involuntary control over the important organs originate in the autonomic system itself. It is evident, therefore, that the autonomic system is essentially a part of the peripheral system. The autonomic system reaches its highest development in man and the mammals generally, where it is found to consist of two distinct conducting units, namely, the sympathetic division and the parasympathetic division. (Fig. 128.)

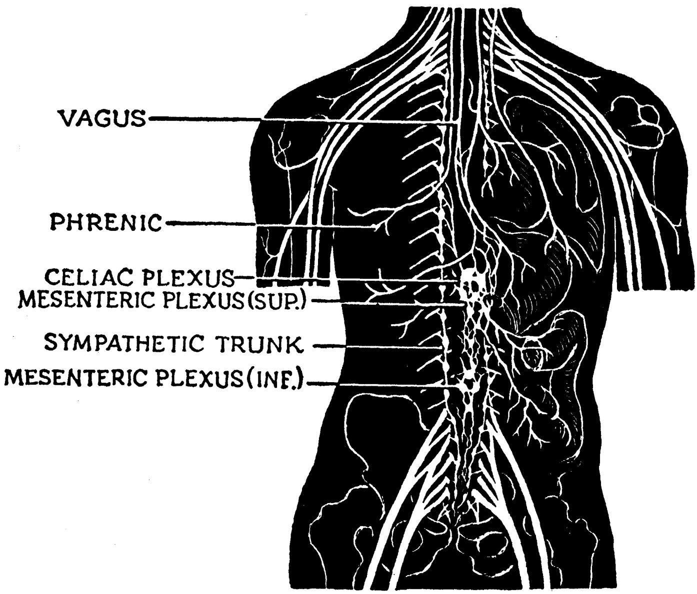


FIG. 128.—The general plan of the autonomic nervous system in man. *Cf.* Fig. 129.

Sympathetic Division.—The sympathetic division consists essentially of a pair of delicate nerve cords which lie exposed in the thoracic and abdominal cavities, one on each side of the vertebral column, close to the dorsal body wall. Examination of these sympathetic cords show that each consists of a rather loosely connected chain of segmental bead-like nerve centers, the sympathetic ganglia. Each sympathetic chain starts anteriorly in the neck region and extends to the posterior part of the abdominal cavity. Each of the constituent sympathetic ganglia receives one or more branches, containing efferent motor fibers, from the nearest spinal nerve shortly after the latter leaves the spinal cord. These connecting efferent fibers, which come from the spinal nerves and extend to the sympathetic ganglia, are known as the

preganglionic fibers. Another group of sympathetic fibers, mostly nonmyelinated, have their origin in the sympathetic ganglia where they synapse with the preganglionic fibers and then extend to the tissues to be innervated. This latter group constitutes the *postganglionic fibers.* (Fig. 129.)

The postganglionic fibers may proceed directly from the sympathetic ganglia to the peripheral tissues, as just indicated, or the

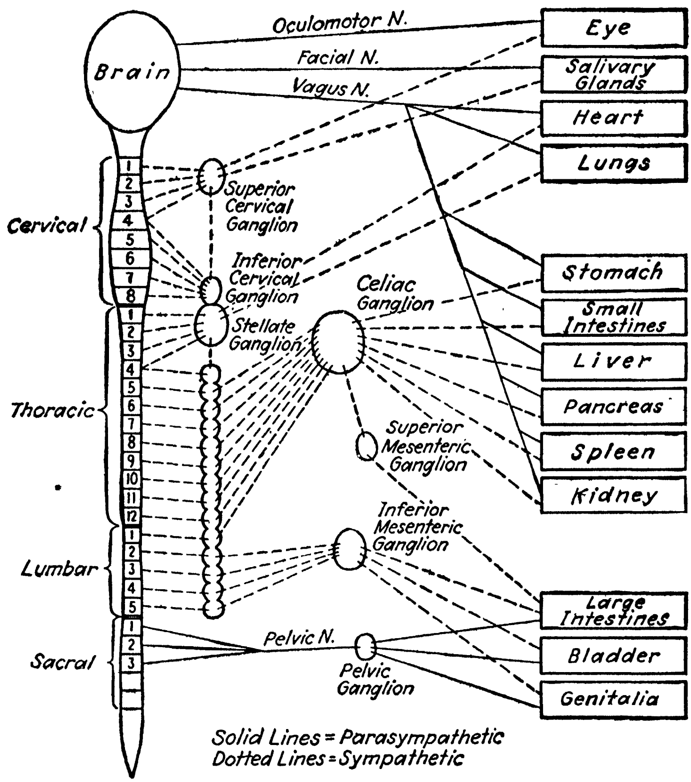


FIG. 129.—Scheme illustrating the distribution of the autonomic nervous system of man and the important plexuses (Celiac Ganglion, etc., etc.) (*Watkeys, Daggs.*)

postganglionic fibers from a number of ganglia may be associated to form an intermediate relay station, or nerve plexus, which is connected to the effectors by a third fiber group. There are several plexuses of varying size and importance in the sympathetic division, but the largest is the celiac ganglion, or solar plexus, from which fibers innervate the important abdominal organis, including the stomach, intestines, liver, pancreas, and certain parts of the urogenital system.

Parasympathetic Division.—The parasympathetic division of the autonomic nervous system consists of efferent fibers which arise in the extreme anterior and posterior portions of the central nervous system. The anterior parasympathetic fibers are given off from certain neuronic areas lying in the midbrain and the hindbrain, whereas the posterior parasympathetic fibers have their origin in the sacral portion of the spinal cord. The parasympathetic fibers extend directly from their points of origin in the central nervous system to the tissues that they innervate, and there they form synapses with the postganglionic fibers of the sympathetic division. In general, intermediate ganglia are not present as in the sympathetic elements. (Fig. 129.)

The basic effect of the mammalian autonomic system is to supply the involuntary and cardiac muscles and also the glands with a dual control through the double innervation by sympathetic and parasympathetic fibers. Altogether, the elements of the autonomic system innervate and exercise involuntary control over the smooth muscle tissue present in all the organs and organ systems of the vertebrate body, including, in addition to those already noted for the sympathetic division, such diverse structures as the pupil of the eye, the lungs, the heart, vascular system, and all types of gland, among which, of course, are those of the endocrine system. In addition it is known, in certain instances at least, that the autonomic system is also equipped with sensory fibers capable of transmitting afferent impulses from the innervated effectors, as in the case of pain stimuli, to the central nervous system. The pain stimuli from the viscera are not definitely localized as a rule and may be referred to other regions of the body.

An additional fact of great functional importance—associated with the dual control of the sympathetic and parasympathetic divisions—is based on experimental studies which have shown that the sympathetic and parasympathetic divisions of the autonomic system are essentially antagonistic in their control of various organs. Thus, to take a well-known example, the stimulation of the sympathetic fibers that innervate the muscle tissue of the heart and also of the blood vessels results in an increased activity of the heart and a contraction of the muscle tissue in the walls of the blood vessels. This causes an increase in the blood pressure. Contrariwise, stimulation of the parasympathetic fibers innervating these vascular tissues results in a slowing down of the heart action, a dilation of the blood vessels, and a consequent fall in blood pressure. That the action of the sympathetic and parasympathetic divisions may be reversed in other regions can be seen, for example, when the sympathetic fibers innervating the

bronchi of the lungs are stimulated, for, in this organ, the sympathetic impulses cause a relaxation of the muscle fibers rather than a contraction as noted above in the vascular system, while the stimulation of the parasympathetic fibers innervating these tissues causes a contraction of the muscle tissue, which, again, is the reverse of its action in the vascular system.

It is clear, therefore, from the experimental evidence, that the action of the sympathetic and parasympathetic divisions in a particular organ is antagonistic and, furthermore, that their action is not uniform in the various innervated organs. Although a great deal remains unknown about the functioning of the autonomic system with its tremendously complex interrelationships, the data are more than sufficient to show that it is of supreme functional importance in maintaining tireless, efficient, and involuntary control over an almost infinite number of details associated with the proper and continuous functioning of the important organ systems.

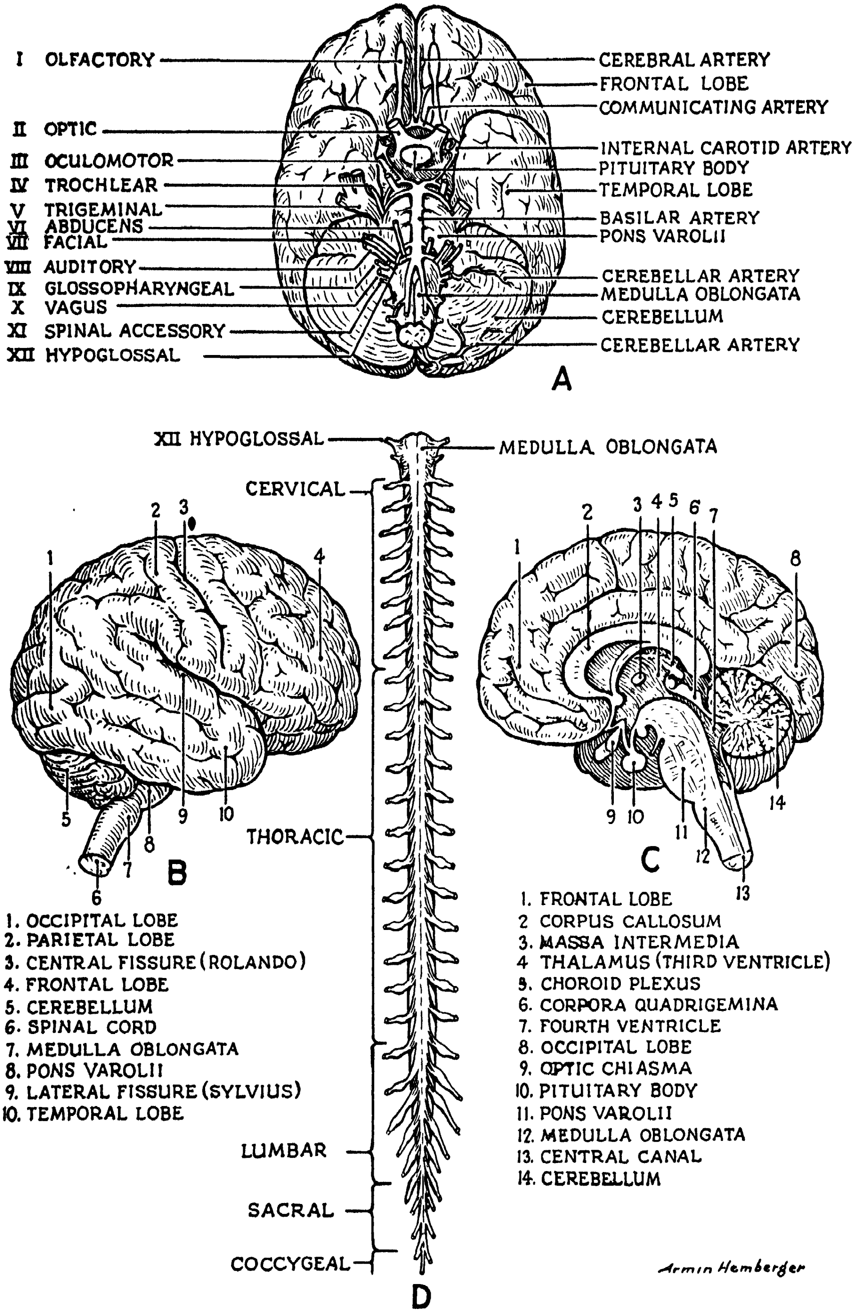


Plate XIV.—Central nervous system of man. *A*, general structure as seen from the under surface; *B*, right side of the brain; *C*, median sagittal section showing the cut surface of the right half of the brain; *D*, spinal cord with the roots of the paired spinal nerves.

CHAPTER XI

BIOLOGY OF THE NERVOUS SYSTEM (II)

THE CENTRAL NERVOUS SYSTEM

At long last our consideration of the various units of the human nervous system brings us to the central nervous system, consisting of the brain and spinal cord, which is the supreme structural and functional unit not only of the complete nervous system but of the entire body as well. It is clear that the sensory, peripheral, and autonomic divisions of the nervous system are of functional importance only because of their association with the central nervous system. Every sensation received by the various specialized sense organs from the internal and external environment is sent to the central nervous system for interpretation and for the determination of the proper action to be taken by the organism. The nervous impulses that speed continuously over the network of peripheral and autonomic nerves are directed either to (afferent) or from (efferent) the brain and spinal cord.

We have seen earlier that the vertebrate nervous system starts in the embryo by the formation of a thin-walled ectodermal tube which gradually becomes differentiated to form the exceedingly intricate adult nervous system. The numerous neuronic descendants of the pioneer ectodermal nerve cells become the highly differentiated neurons of the adult brain and spinal cord. These pioneers never leave the chosen land, and, protected and obeyed by the lesser members of the body, their decisions constitute the law of the bodily domain. Thus we have the primary structural and functional fact that the central nervous system is the cellular unit of the entire nervous system, for the neurons lie actually within the brain and the spinal cord or in the closely associated sensory ganglia which are situated on each of the sensory nerve roots close to the spinal cord. Structurally, it is possible to divide the neurons into two main cell types, namely, the bipolar type and the multipolar type. Present in both types of neuron and, therefore, a characteristic feature of the neuronic type of cell structure is the prolongation of the cell cytoplasm into two or more processes, the nerve fibers, which are the specialized agents for conduction, as has previously been seen in the study of the peripheral system. From

the functional standpoint, the neuronic cell processes, as shown above, are divided into the dendrites, which carry impulses into the cell body, and the axons, which carry impulses from the cell body to the peripheral regions (page 240). The bipolar neuron possesses one dendrite and one axon, while the multipolar neuron typically possesses numerous dendrites and one axon; the latter may give off numerous branches. (Fig. 130.)

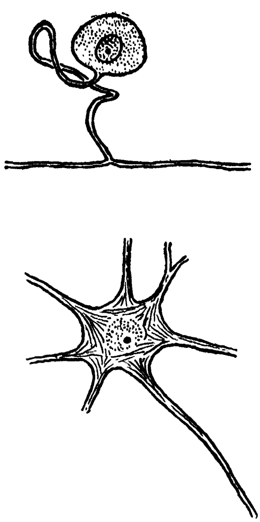


FIG. 130.—Diagrams of bipolar (*above*) and multipolar (*below*) neurones. Highly magnified. *Cf.* Fig. 131.

The bipolar neurons are present in the sensory ganglia of the cranial and spinal nerves and also in the retina. Thus they show considerable structural diversity, but it is clear that they are fundamentally bipolar, each neuron having a separate dendrite and axon. In the fully formed bipolar cell, the axon and dendrite are usually fused together near the cell body so that the cell appears to be unipolar. If, however, the single axon-dendrite process is traced some distance from the cell body, it will be found to split to form a T-shaped process with the pear-shaped cell body attached to the base of the T.

The multipolar neuron is the typical motor neuron present in the spinal cord and in the cortex of the brain. As seen in the spinal cord, the multipolar neuron has a large cell body with numerous short dendrites and a long myelinated axon. The axon usually gives off some tiny branches (collaterals) near the cell body and then continues out of the cord, along with other associated fibers, to form an efferent division of a spinal nerve. In the motor areas in the cortex of the brain the multipolar cells, reaching their climax in the large pyramidal cells, are subject to wide structural variation characterized in part by profuse branching of the axons and the dendrites. It is presumed, but not proved, that the primary functional differentiation between dendrite and axon in direction of impulse persists throughout the nervous system. Since several billion neurons are present in the central nervous system of man, it is readily seen that the actual tracing of an almost infinite number of microscopic nerve fibers is an impossible task. (Fig. 131.)

Neuron Histology.—The protoplasm of the neuron is largely lacking in structural features at the level of microscopic visibility that give any indication of its functional ability. The nucleus is large

and well formed and contains one or more prominent nucleoli but, on the whole, is quite unexceptional in appearance. The cytoplasm, however, is at times fibrillated to form numerous very fine intracellular fibers, the neurofibrils, which permeate essentially all regions of the cytoplasm but particularly in the region around the nucleus. Toward the periphery of the cell the neurofibrils tend to be in parallel lines, thus forming bundles of neurofibrils which extend out into the axon and dendrite. Apparently there is little doubt that these fibrillar elements are directly concerned with the transmission of the nervous impulses to and from the cell bodies of the neurons. Another cytoplasmic feature is noted in the presence of the chromophil substance, so termed because of its reaction to the stains. In most of the neurons, the chromophil substance is widely distributed throughout the cell cytoplasm and out into the dendrites, but it is not present in the axons. Possibly the chromophil substance is stored nutritive material, but no proof exists of either its nature or function. Possibly even more obscure in its functional characters, but prominent structurally, is the net-like reticular apparatus (Golgi body) lying close to the nucleus. (Fig. 131.)

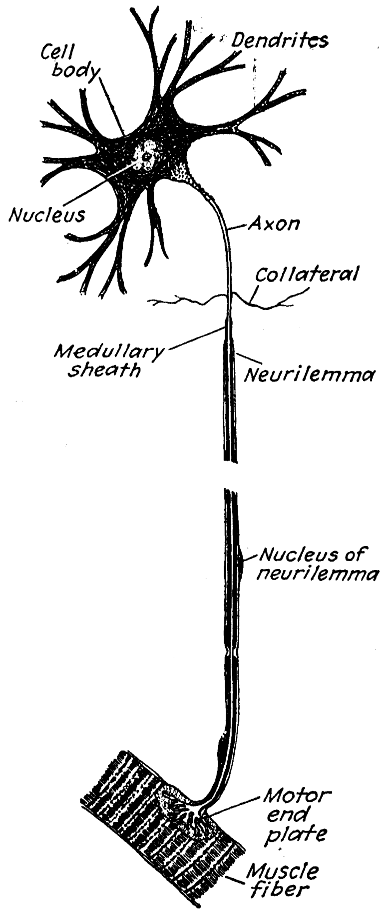


FIG. 131.—Diagram of a typical multipolar motor neuron with a medullated axon. (*Wolcott.*)

One of the most important features of the neurons is the terminal branching, or arborization in the region where the connection (synapse) with the nerve fibers of another cell is made, or where the cell processes end in the tissues of the peripheral effectors. Considering, first, the synapses through which a nervous impulse is passed from the axon of one neuron to the dendrite of another, the best evidence is that the processes of the synapsing cells are not actually fused with each other but are only in close apposition. It can be shown in many instances

that the region of the synapse is plentifully supplied with vascular elements, a condition indicating that it must be a region of high metabolic activity. Again it should be pointed out that the enormous number of neurons, each with several synapses of microscopic dimensions, constitute a system of incomparable complexity in which it is possible only to get an idea of the main outlines and never to trace out the impulse routes and synapses of the individual cells.

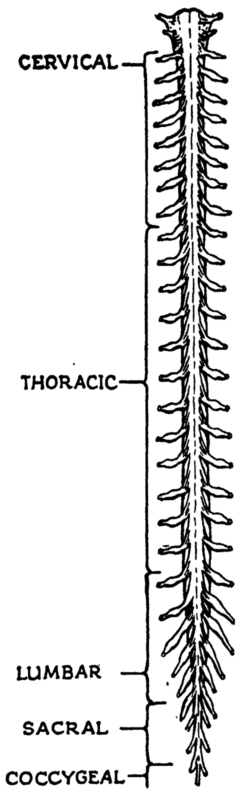


FIG. 132.—Human spinal cord with the roots of the paired spinal nerves. Compare with the spinal cord shown in Plate 12*A*. Diagrammatic.

THE SPINAL CORD

The spinal cord may be said to extend from the foramen magnum at the base of the skull, where it merges into the brain, to near the posterior end of the vertebral column, where it shades off into a fine terminal filament (filum terminale), the latter continuing into the sacral region of the vertebral column. The spinal cord proper is thus some 17 or 18 in. long, about ¾ in. in diameter, and weighs less than 2 oz. It is fairly cylindrical in shape and with two enlarged areas, one of which is in the shoulder region where the spinal nerves arise that innervate the arms, whereas the other is in the sacral region where the spinal nerves innervating the legs leave the cord. It has already been noted in the description of the peripheral system that 31 pairs of spinal nerves, each with a posterior sensory root and an anterior motor root, leave the cord at essentially regular intervals throughout its length, corresponding to the segmentation of the vertebral column that encloses it. (Fig. 132.)

We may now trace the roots of a spinal nerve into the interior of the cord and thereby get a conception of the internal arrangements. This can only be accomplished by the microscopic examination of a transverse section of a suitable spinal cord. The study of a section of the cord shows it to be roughly circular in outline but with a considerable anteroposterior flattening. A rather deep indentation occurs on the ventral surface (anterior fissure), and a shallow indentation on the dorsal surface (posterior fissure). If these fissures were extended, they would meet in the center of the cord and thus divide it into

symmetrical right and left halves. The transverse section of the cord reveals also a clear division of the tissues into an inner portion, the gray matter, which is enclosed by an outer portion of white matter. The gray matter is roughly H-shaped, with the crossbar of the H pierced in the center by the tiny central canal, which is thus in the exact center of the cord. The central canal is the minute remnant of the original large central cavity of the thin-walled embryonic neural

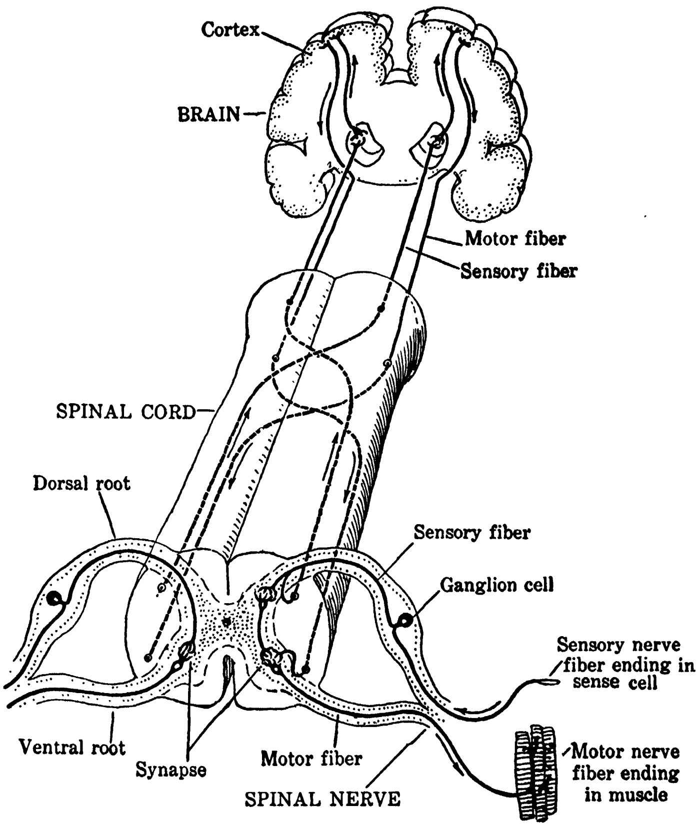


FIG. 133.—Illustrating the origin of the spinal nerves and the sensory and motor nerve paths in the spinal cord, leading to the cortex of the brain. (*Woodruff.*)

tube. The white matter of the cord completely encloses the inner H-shaped mass of gray matter. (Fig. 133.)

Spinal Cord Histology.—Further study of the spinal cord reveals the important fact that the gray matter is cellular and composed of neurons, whereas the white matter consists entirely of myelinated nerve fibers (axons and dendrites) extending up and down and across the cord. Furthermore, it is seen that the roots of each spinal nerve

are directly connected to the inner gray matter of the cord, the afferent sensory roots joining the dorsal (posterior) ends of the uprights of the H and the efferent motor roots joining the ventral (anterior) ends. The ventral horns are larger and project more deeply into the white matter, and in them are the large efferent multipolar motor neurons, the axons of which converge segmentally to form the ventral roots of the spinal nerves. In the smaller dorsal horns of the gray matter lie the multipolar association neurons with their numerous dendrites and axons. Through the dendrites of the association neurons, the afferent sensory impulses are received in the cord by means of synapses with the axon fibers of the sensory roots. These sensory impulses are then transferred to the dendrites of the motor neurons at the same level of the cord or, more frequently, at a different level. In the latter case, the sensory impulse received in the cord must be passed up or down the conducting fiber tracts until the synapse is made with the dendrites of the motor neurons innervating the desired muscles. And it may also be necessary that the incoming sensory impulses be conducted to the brain before the proper adjustment with the motor system can be determined.

Fiber Tracts.—One of the notably difficult and important problems in studying nerve function has been the localization of conduction in the spinal cord to particular fiber bundles in the white matter. Though it is impossible to trace single nerve fibers in the white matter to individual neurons in the gray matter, it has nevertheless been found possible to identify bundles of fibers (fiber tracts) which connect with definite neuronic areas. This was accomplished experimentally by sectioning the spinal cord in various experimental animals and thus separating certain neuronic areas of the brain and spinal cord from the connected nerve fibers. When this is done, it has been found possible sometime later to trace the paths of degeneration of the nerve fibers up and down the cord by microscopic study of prepared material. This results from the fact that, when the neurons are separated from the fibers, it invariably follows that the fibers soon degenerate. The fibers (which, after all, are only cell processes) are unable to nourish themselves or to maintain independent life activities when separated from the cell bodies. Studies on degenerating areas of nerve fibers, following separation from the neurons, has consistently revealed the presence of definite fiber tracts in the white matter of the injured cord. The fiber tracts in the spinal cord can be grouped into (1) the ascending fiber tracts, which carry impulses up the cord toward the brain from the peripheral regions, and (2) the descending fiber tracts, which carry impulses down the cord, away from the brain.

In essence, of course, the ascending tracts carry sensory impulses to the brain, and the descending tracts carry motor impulses from the brain or from posterior regions of the central nervous system to the effectors. (Fig. 134.)

Afferent Fiber Tracts.—The main ascending afferent fiber tracts in the spinal cord include (1) those which carry the proprioceptive impulses from the muscles of the body to the motor areas in the cerebral cortex of the forebrain. These fiber tracts occupy a considerable area in the posterior central portion of the cord. They lie above the "connecting bar" and between the "uprights" of the H-shaped area of gray matter, continuing to the periphery of the cord on each side of

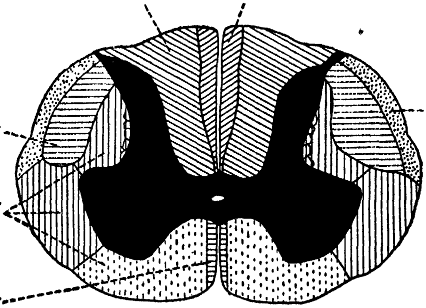


FIG. 134.—Diagram of a transverse section of the spinal cord to show the general arrangement of the white and gray matter (heavy black area) and the localization of some of the important fiber tracts. Fiber tracts in the *fasciculus cuneatus* and *fasciculus gracilis* carry the afferent conscious proprioceptive impulses, whereas the dorsal *spino-cerebellar tracts* carry the afferent unconscious proprioceptive impulses. The crossed pyramidal fibers (efferent) are located in the *lateral corticospinal tracts*, and the direct pyramidal fibers are in the *ventral cortico-spinal tracts*. *Cf.* Fig. 133. (*Crandall, "Human Physiology," W. B. Saunders Company. After von Geheuchten.*)

the dorsal fissure. These tracts carry the impulses associated with conscious proprioception. When they are destroyed, the individual loses the muscle sense that enables him to know the position of legs or arms without looking at them. No other route exists for the afferent sensory impulses arising in the muscles, joints, and tendons to reach the interpretive areas in the brain.

Other ascending spinal fiber tracts include (2) those extending from the body muscles to the cerebellum of the hindbrain. These tracts lie on the right and left sides of the cord, near the periphery and ventral to the tracts just noted above in (1). They transmit the unconscious proprioceptive impulses to the cerebellum, by means of which equilibrium is constantly, but unconsciously, maintained. Finally, the ascending fiber tracts in the cord include (3) those which

carry the impulses from the sensory areas in the skin, associated with the various skin sensations. In one group of these paired tracts, afferent impulses associated with the sensations of pain, heat, and cold pass upward, and, in the other group, impulses associated with the tactile senses appear to be segregated. These are relatively small tracts located ventrally in the cord; the tactile fiber tracts lying close to and on each side of, the ventral fissure, whereas the other pair of sensory tracts are situated just below the cerebellar tract indicated in item (2) above. The afferent impulses from the important sense organs located in the head enter the brain directly over the corresponding spinal nerves without association with spinal cord elements.

It should be understood that the sensory impulses coming into the cord through the posterior roots of the spinal nerves are not necessarily transmitted to the brain in all cases. For example, the afferent impulses associated with relatively simple reflexes may be transmitted up or down the cord to the proper level for synapse with a particular group of motor neurons. Here they are routed over the synapsing association neurons of the cord and then over the axons of the motor neurons to the effectors. Thus, as in a frog, the brain may be entirely destroyed, but the reflex activity for the posterior portion of the body will remain intact, so that irritation of the sensory elements in the skin will produce reflex actions in the limbs.

Efferent Fiber Tracts.—The descending, or efferent, fiber tracts of the cord have their origin, for the most part, in certain neurons located in the cerebral cortex of the brain and, accordingly, are known as the *corticospinal pathways.* All along the cord, the terminal arborizations of the axons of these tracts synapse with the dendrites of the motor neurons in the anterior horns of the gray matter. Passing posteriorly from the brain cortex, the corticospinal fibers reach the posterior portion, or medulla, of the hindbrain. In this region, about three-fourths of the descending fibers pass over to the opposite side of the cord (decussation); that is, the fibers coming from the right side of the cortex find their way to the left side of the cord and vice versa. (Fig. 133.)

These decussating fibers of the corticospinal pathways form the crossed pyramidal tracts. They are situated in the cord between the areas of the ascending cerebellar tracts and the outer boundaries of the gray matter, to the right and left of the ventral fissure. The remaining one-fourth of the corticospinal fibers do not cross over in the medulla but enter the spinal cord on the side corresponding with their origin and accordingly constitute the uncrossed, or direct pyramidal tracts. As a matter of fact, however, the fibers of the direct pyramidal tracts also cross to the opposite side of the cord but not until they

reach the various levels where synapse is made with the motor neurons. Consequently, it appears that all corticospinal fibers innervate the opposite side of the body from that of their cerebral origin. The significance of the crossing of the nerve fibers, which is a basic feature of the vertebrate nervous system, is not apparent. (Fig. 133.)

Over the crossed and the direct pyramidal tracts of the spinal cord flow the efferent nervous impulses from the brain cortex which initiate voluntary movement throughout the body. Unconscious (involuntary) control of the muscle tissues, associated with muscle tonus, equilibrium (in response to afferent impulses received from the semicircular canals and proprioceptive impulses), and various other vital activities, notably gland secretion, are the functions of two groups of neurons situated in the midbrain and in the hindbrain respectively—the latter group being situated near the vestibular division of the auditory nerve which innervates the semicircular canals.

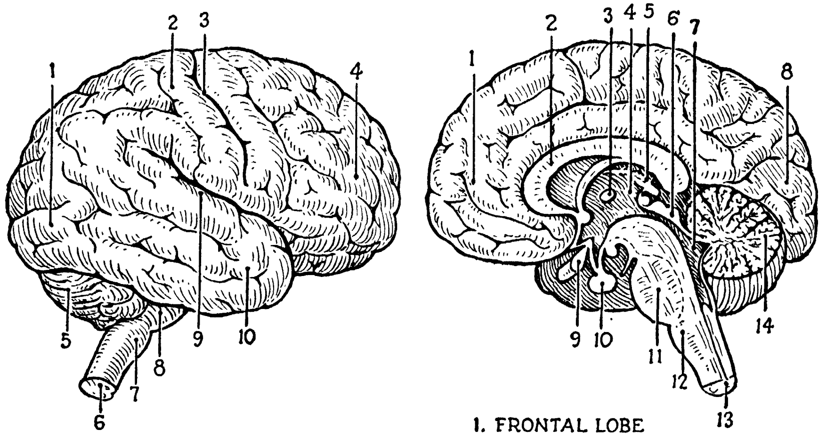
The fiber tracts of the important pathways for involuntary control, although not so large as those previously mentioned, have been clearly located. The cerebellar tracts are situated on each side of the spinal cord in close proximity to the outer anterior border of the crossed pyramidal tracts, whereas the fiber tracts from the midbrain lie at the anterior edge of the cord between the ascending sensory fiber tracts. The size of the fiber tracts decreases as they extend posteriorly in the cord, for, as would be expected, the maximum number of afferent and efferent fibers in each tract are brought together just posterior to the medulla. (Fig. 134.)

The Brain

The spinal cord passes through the *foramen magnum* at the base of the skull and at once merges into the medulla of the hindbrain. The brain as a whole may be regarded as consisting of two main regions. There is, first, the primitive underlying brain stem which appears essentially as an enlarged and differentiated projection of the spinal cord, ending anteriorly with the midbrain and posteriorly with the medulla of the hindbrain. The brain stem is essentially a bottle-neck through which must pass the millions of afferent and efferent fibers connecting the brain neurons with the body as a whole. On reaching the forebrain, the fibers are concentrated into a small area, or internal capsule, of the forebrain from which they spread out (corona radiata) into the comparatively large spaces (external capsule) of the cerebrum. Secondly, a much larger superstructure lies above the brain stem which consists of the forebrain (cerebrum) and the cerebellum of the hindbrain. The forebrain has been aptly described as "the flowering of the brain stem." Using botanical terminology, the

spinal cord may be thought of as a tree-like structure, from which the branching spinal nerves emerge for connection with every body structure. (Fig. 135.)

It was previously stated that the brain and the spinal cord develop through the differentiation of a thin-walled ectodermal tube during early development. The amazing structural and functional changes



1. OCCIPITAL LOBE
2. PARIETAL LOBE
3. CENTRAL FISSURE (ROLANDO)
4. FRONTAL LOBE
5. CEREBELLUM
6. SPINAL CORD
7. MEDULLA OBLONGATA
8. PONS VAROLII
9. LATERAL FISSURE (SYLVIUS)
10. TEMPORAL LOBE

A

1. FRONTAL LOBE
2. CORPUS CALLOSUM
3. MASSA INTERMEDIA
4. THALAMUS (THIRD VENTRICLE)
5. CHOROID PLEXUS
6. CORPORA QUADRIGEMINA
7. FOURTH VENTRICLE
8. OCCIPITAL LOBE
9. OPTIC CHIASMA
10. PITUITARY BODY
11. PONS VAROLII
12. MEDULLA OBLONGATA
13. CENTRAL CANAL
14. CEREBELLUM

B

FIG. 135.—Drawings of the human brain. *A*, external view of the right side; *B*, median sagittal section, showing the cut surface of the right half of the brain.

that occur before the adult stage is reached are due, first, to increases in the number and the degree of differentiation of the neurons of the primitive neural tube and, second, to the development of the protoplasmic processes (axons and dendrites) from the cell bodies. These make the proper connections with those other neurons and gradually become associated in the fiber tracts of the brain and spinal cord and also in the cranial and spinal nerves with their receptor and effector connections. These neuronic associations, involving ever increasing complexity, culminate in the human brain.

Divisions of the Brain.—In the human brain the primary divisions into forebrain, midbrain, and hindbrain are apparent as in the brain of vertebrates generally, but such a marked structural and functional development of the cerebral hemispheres in the forebrain has occurred that the other two primary brain divisions are greatly overshadowed.

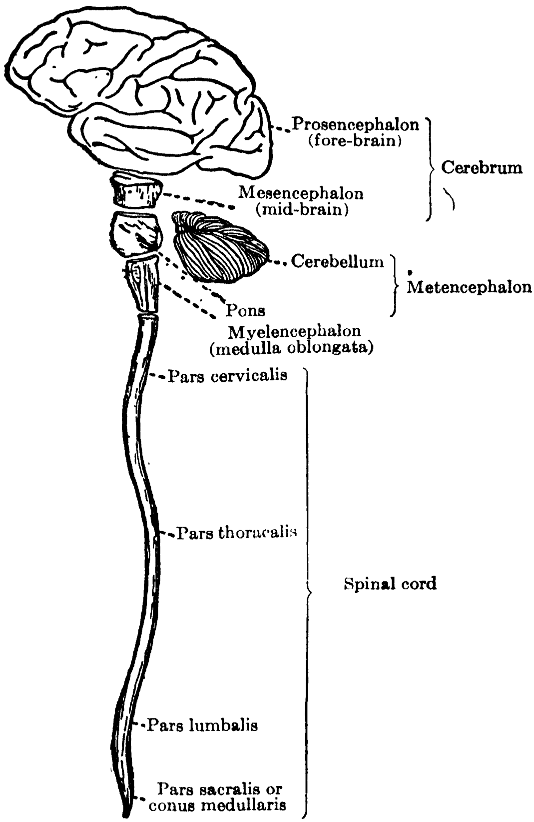


FIG. 136.—The main divisions of the human central nervous system shown separately. Left side. Diagrammatic. (*Morris, "Human Anatomy," P. Blakiston's Son & Company, Inc.*)

Thus the complete human brain of an average sized male adult weighs in the neighborhood of 50 oz. Of the total weight, approximately nine-tenths is due to the cerebral hemispheres. The remaining 5 oz. are divided between the midbrain and hindbrain, with the latter much the larger, so that the midbrain is very small indeed. In viewing the brain from the upper, or dorsal, surface only the paired cerebral hemispheres are seen, for they are large enough completely to cover over the other portions. This overgrowth of the forebrain is par-

ticularly striking when one compares the brain of man with the brain of a lower vertebrate, such as the frog, in which a dorsal view reveals the three primary divisions of the brain arranged in a linear fashion and merging posteriorly into the spinal cord. (Fig. 136.)

From the functional standpoint, the neurologist finds that the two main divisions of the human brain are the forebrain and the hindbrain, with the midbrain functioning in the main as a fiber tract and apparently without major independent integrating functions of its own. The *midbrain* is seen in gross structure as a short section of the underlying brain stem situated between the fore- and hindbrain. On the under surface of the midbrain region are two rounded, pillar-like prominences, the crura cerebri, a term that literally means the "legs of the cerebral hemispheres," and so named because the latter seem to rest upon them. As a matter of fact, the crura cerebri are fiber tracts with connections extending to the forebrain. The dorsal surface of the midbrain shows four rounded projections, the corpora quadrigemina, which are also important neurological landmarks because of their fiber tracts.

Hindbrain.—The *hindbrain* consists of three main portions: the medulla oblongata, the pons (pons Varolii), and the cerebellum. Of these, the medulla is the most posterior part of the brain stem and, as stated above, joins the anterior end of the spinal cord. Viewed from the ventral surface, the medulla appears as an enlarged portion of the spinal cord. Viewed dorsally, it is found to possess a triangular cavity, the fourth ventricle, which is continuous with the central canal of the spinal cord. The ventricle is covered by a thin membrane. The lateral walls and floor of the medulla contain important fiber tracts and, in addition, contain neuronic areas which exercise involuntary control over such vital functions as respiration, heart action, blood pressure, and various complex reflex actions of a more difficult nature than those handled by the neurons in the spinal cord. Partially covering the anterior portion of the medulla, as seen from the ventral side, and extending along the brain stem to the midbrain is the pons, which consists almost entirely of two main groups of nerve fibers, designated as the *longitudinal tracts* and the *transverse tracts.* The latter appear from the ventral surface as a ring-like structure surrounding the brain stem and connecting dorsally through the middle peduncle with the cerebellum lying above the brain stem. (Figs. 135*B*; 136.)

Thus the transverse fiber tracts of the pons make possible a close functional association of the three divisions of the hindbrain (medulla, pons, and cerebellum). Of these, the cerebellum is the largest and possibly the most important unit. It is a trilobed structure with right,

left, and median portions, held in position and connected with the other elements of the nervous system by three fiber tracts, one of which, the middle peduncle, consists of the transverse fibers from the pons. The superior peduncle extends directly anteriorly into the cerebrum, while the inferior peduncle runs posteriorly, connecting with certain fiber tracts of the spinal cord. (Fig. 140.)

The cerebellum is a very important brain center for the control of personally acquired reflexes and for general supervision over muscular movements, particularly those associated with equilibrium. Many of the afferent fibers from the sensory structures of the body form synapses in the cerebellum, and it is apparent that it has a wide range

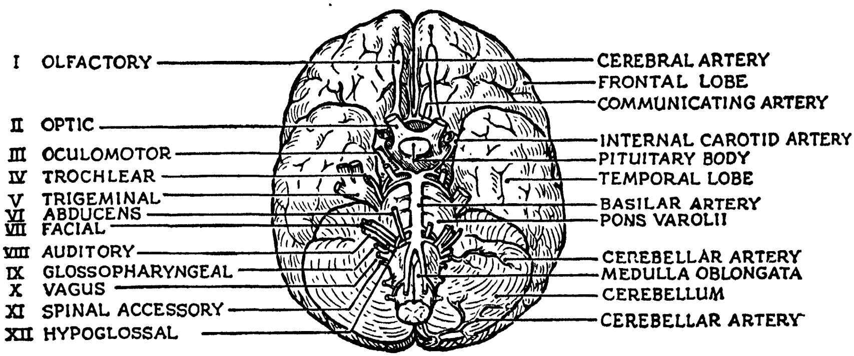


FIG. 137.—The human brain viewed from the under surface. Roots of the cranial nerves shown to the left.

of influence on both sensory and motor impulses passing to and from the forebrain. No conclusive evidence appears to exist, however, that the cerebellum acts otherwise than in a subsidiary manner to the higher nerve centers of the forebrain.

Before passing to a consideration of the forebrain, it will be well to indicate the important relationships between the hindbrain and the 12 pairs of cranial nerves, for all but the first two pairs of cranial nerves emerge from the hindbrain. All of the cranial nerves have their real origin in definite neuronic areas[1] which are located, with the exception of the first pair (olfactory), in the midbrain and hindbrain. The neuronic areas, located deeply in the brain tissue, may be some distance from the point where the nerves emerge from the brain.[2] (Fig. 137.)

[1] Neurologists commonly refer to the neuronic areas as nuclei, but the use of the term *nuclei* in this connection is somewhat confusing to the biology student. The term *neuronic area* is therefore preferable, indicating an area in which a great many of the nucleated cell bodies of the neurons are concentrated.

[2] Consult Appendix: Cranial Nerves.

Forebrain.—The forebrain, or cerebrum, greatly overshadows all other parts of the brain in its functional aspects and is clearly the superorgan of the human nervous system. The cerebrum consists primarily of a pair of cerebral hemispheres, with which three lesser structures are associated, namely, the olfactory lobes, the thalami, and the corpora striata. The olfactory lobes, as the name indicates, are concerned with the sense of smell. In some of the lower vertebrates they are very highly developed and constitute the largest part of the forebrain. In man, they are of comparatively small size, lying underneath and near the anterior border of each cerebral hemisphere. Just below this position is the sensitive area of the nasal epithelium, separated from the brain cavity by the bony perforated cribiform plate. Through the latter great numbers of minute sensory nerve fibers from the olfactory lobes project into the nasal cavity and innervate the nasal epithelium (page 220).

The thalami (optic thalami) consist of a pair (one for each cerebral hemisphere) of neuronic areas deeply embedded in the tissue of each cerebral hemisphere, close to the median line and near the midbrain region of the brain stem. As will be seen later, the thalami are important association centers for synapses with afferent fibers connecting with the forebrain—particularly with respect to the so-called body-sense (pain, warmth). Another pair of neuronic areas present in the forebrain are the corpora striata which are situated in close proximity, lateral and anterior to the thalami. The corpora striata are concerned as association areas for synapses with efferent fibers from the forebrain controlling muscle action.

Cerebral Cortex.—An examination of the outer tissue layer, or cortex, of the cerebral hemispheres shows an uneven or convoluted surface due to elevations (gyri) and depressions (sulci) which are quite uniformly distributed over the cerebral areas. Four main regions of the cortex can be noted, namely, the frontal, parietal, occipital, and temporal, corresponding in position to the areas of the skull as previously given (page 197). In each cerebral hemisphere the boundaries of the regions just noted are more or less distinctly indicated by conspicuous depressions (fissures) which are deeper than the sulci. Particularly prominent is the fissure of Rolando which marks the boundary between the frontal and parietal lobes and constitutes an important landmark for the study of functional localization in the cortex. It should be said in this connection that the results obtained from numerous experimental studies on cerebral function show beyond a doubt that the neurons concerned with the control of a particular function are localized in definite cortical areas of the cerebral hemi-

spheres. It is possible to indicate only a few of the many important areas that have been identified. In each hemisphere, the area of the frontal lobe lying just anterior to the fissure of Rolando is known to be definitely associated with the control of voluntary muscles in various regions of the body. Thus the muscles of the leg, body, and arms are controlled by neurons in the cortex lying along the anterior margin of the fissure of Rolando, whereas neurons along the posterior margin of this fissure in the parietal lobe serve as interpreters of the afferent sensory impulses which give the tactile sense. In the parietal lobes, posterior to the fissure of Rolando, other neuronic areas are associated with facial control and speech. The auditory center of the cortex is localized near by in the anterior portion of each temporal lobe, and the incoming visual impulses from the retina are received by cortical

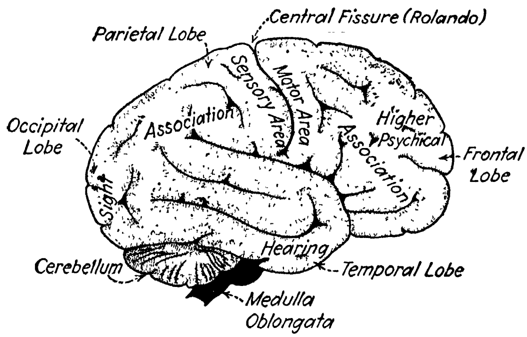


FIG. 138.—Human brain. View of right side showing localization of various important areas in the cortex. (*Watkeys, Daggs.*)

neurons located in the posterior portion of the occipital lobes. (Fig. 138.)

Cerebral Fiber Tracts.—It is apparent that the segregation of certain cerebral functions in definite and corresponding areas of the cerebral hemispheres means that the entire brain is not ordinarily involved in the interpretation of the incoming impulses or in the transmission of the efferent impulses. Thus, to take one example, afferent impulses from the sensory areas associated with the voluntary muscles of the arms and legs on the *right* side of the body are primarily received by neurons in the posterior portion of the frontal lobe of the *left* cerebral hemisphere. But some of the incoming impulses from the peripheral regions may be so important as to require additional consideration, and this will necessarily involve other neuronic areas of the cerebrum. Accordingly, it is found that the various localized neuronic areas in the cerebral hemispheres are interconnected by special *association fiber tracts* composed of bundles of nerve fibers through which the

impulses from one cerebral region are transferred to other regions as required. In the forebrain, separate groups of the association fiber tracts are established for communication between the right and left cerebral hemispheres and also for communication between the various neuronic areas in each of the hemispheres. This condition is easily understandable when one thinks of the telephone central of a large city containing a number of separate functional units, the exchanges, each of which is connected to all the other exchanges in the central office so that messages may be transmitted back and forth throughout the entire switchboard. (Fig. 139.)

In addition to the association fiber tracts, another very important and even more widely distributed system of fiber tracts, the *projection*

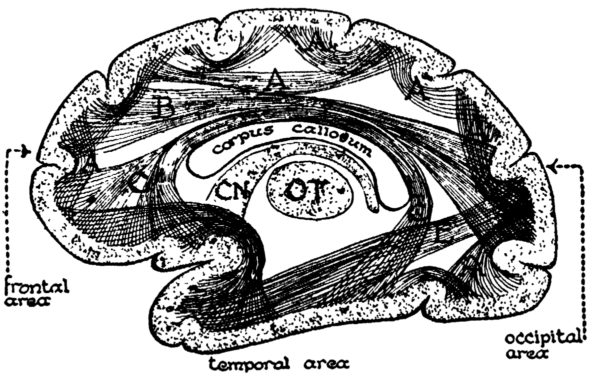


FIG. 139.—Schematic section of the human brain showing the association fiber tracts. *A*, between adjacent areas; *B*, connecting frontal and occipital areas; *C*, *D*, connecting frontal and temporal areas; *E*, connecting occipital and temporal areas. The corpus callosum also contains association fibers connecting the cortex of the right and left cerebral hemispheres. *CN*, caudate nucleus; *OT*, thalamus. (*Hunter, Walter, and Hunter, "Biology," American Book Company. Modified from Starr.*)

fibers, connects important regions of the forebrain, midbrain, hindbrain, and spinal cord into a unified whole. Some of the more important tracts of the projection fibers may now be briefly indicated. (1) In the first place, there is present in each cerebral hemisphere a *cerebro-cortico-pontal* tract which originates from the neurons in the cortex of each frontal lobe and extends posteriorly to the pons of the hindbrain where the constituent axon fibers synapse so that the efferent impulses from the cerebrum reach the cerebellum through the fiber tract of the middle peduncle (page 260). This tract carries efferent impulses, which, since they originate in the frontal neurons, are presumed to be of a very high order. (2) The *pyramidal tracts* originate in the so-called pyramidal neurons of the cortex of the frontal lobes near the fissure of Rolando, pass ventrally through the corpora striata,

and then form the crossed and uncrossed fiber tracts of the spinal cord (page 256). The crossing of the pyramidal tracts occurs in the medulla of the hind brain. The pyramidal tracts transmit efferent impulses for the control of voluntary motion. (Fig. 140.)

(3) The *cutaneous sensory projection tracts,* carrying afferent impulses, originate in the neurons situated in the anterior portion of each parietal lobe and extend to the optic thalami where the main sensory fiber tracts of the spinal cord terminate anteriorly. It should

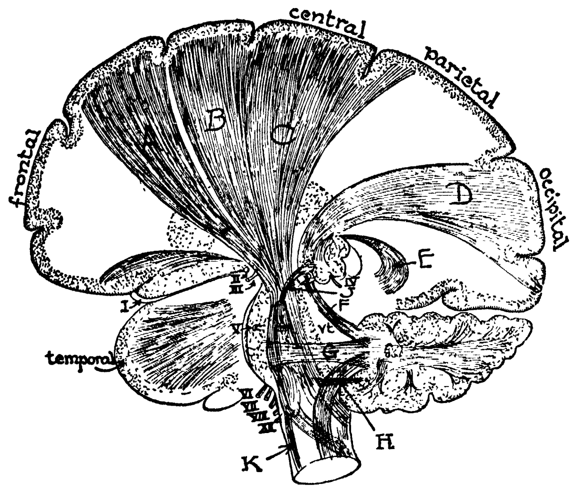


FIG. 140.—Schematic section of the human brain showing the projection fiber tracts connecting the cerebrum and other parts of the brain and spinal cord. *A*, tracts connecting cortex of frontal lobe to the pons varolii and thence to the cerebellum via the transverse fibers (middle peduncle) at *G*; *B*, pyramidal motor tracts; *C*, sensory tracts; *D*, visual tracts; *E*, auditory tracts; *F*, projection fibers (anterior peduncle) connecting cerebellum and anterior portions of the brain; *G*, transverse fibers of pons varolii; *H*, projection fibers (posterior peduncle) connecting cerebellum and the spinal cord; *J*, projection fibers between auditory nucleus and the brain; *K*, crossing over (decussation) of pyramidal motor tracts in the brain; *Vt*, fourth ventricle. Roman numerals refer to cranial nerves. (*Hunter, Walter, and Hunter, "Biology," American Book Company. Modified from Starr.*)

also be remembered that a crossing of these sensory fibers occurs in the hindbrain, just anterior to the decussation of the pyramidal tracts. (4) The *visual tracts* originate from neurons lying in the posterior part of the occipital lobes and extend posteriorly to special neuronic areas in the midbrain where synapse is made with the afferent fibers of the optic nerves, carrying impulses from the retina. It is probable that each visual cell in the retina has a direct connection through this projection path to one or more cerebral neurons where the interpretation of the visual images takes place. (5) The *auditory tracts* originate

in the neurons of the temporal lobes of the cerebrum from which each extends to neuronic areas located in the midbrain. Here synapse occurs with the fibers of the auditory nerve transmitting auditory impulses from the hindbrain. The routes of the afferent impulses from the cochlea and semicircular canals are difficult to trace through the intricate fiber tracts of the hindbrain and midbrain, but the course of the auditory tracts from the temporal lobes tó the midbrain is well established. (6) Finally, the projection tracts include the superior, middle, and inferior *peduncles* of the cerebellum, concerned with the transmission of impulses to the forebrain, to the midbrain, and to the pons and medulla of the hindbrain, as has been indicated previously (page 261). (Fig. 140.)

Histology of the Cortex.—In the previous study of the spinal cord, it was noted that the gray matter, composed essentially of the motor and association neurons, formed an H-shaped body in the interior of the cord which was enclosed by a layer of white matter consisting of the fiber tracts. This same arrangement of the white and gray matter persists in the medulla, pons, and midbrain, but it is reversed in the cerebellum of the hindbrain and in the cerebral hemispheres of the forebrain, in both of which the gray matter, containing the neurons, forms the outer cortex, while the fibrous white matter is enclosed in the interior. It is this cortical gray matter in the cerebral hemispheres and the cerebellum that constitutes the dominant, controlling, integrative, and interpretive tissue of the body, the seat of consciousness and intelligence. Histological studies of cortical tissue reveal essentially the same general arrangement of tissues throughout. Forming the thin outer covering is the molecular layer, about 0.01 in. thick, consisting largely of interlacing nerve fibers but also containing numerous comparatively small neurons. Below the molecular layer are several nuclear layers composed of various specialized types of neurons. As might be expected, the vascularization of the gray matter is much greater than that of the white matter.

The cortex of the cerebral hemispheres, which is somewhat more highly differentiated than that of the cerebellum, may be subdivided into four or even more rather well-defined layers in correspondence with the various types of neuron that are present. Characteristic structural features are evident in the neurons from different regions of the cortex. Thus in the cortex of the cerebral motor area of the frontal lobes are found the multipolar *pyramidal neurons*, the axon fibers of which form the crossed and uncrossed pyramidal tracts. The pyramidal neurons are the largest neurons in the entire nervous system and almost reach naked-eye visibility. On the other hand, in the

visual area of the cortex the pyramidal type of neuron is almost entirely absent. It is estimated that between 13 and 14 billion neurons are present in the cerebral cortex of the human brain, which, with the associated dendrites and axons, make a complexity of organization which defies complete analysis. A further complication is found in the specialized supporting tissue (neuroglia) which is widely distributed throughout the neurons and fiber tracts of the central nervous system. The neuroglia (literally, nerve glue) cells are of various types but all are characterized by the presence of cellular processes of varying number and complexity which are intermingled with the true nerve fibers in many cases.

Brain Ventricles.—The central cavity of the embryonic neural tube is comparatively large at first but during development is gradually reduced in size as the walls are thickened by the increased number of neurons. Remnants of the original cavity persist as (1) the tiny central canal in the spinal cord and (2) the much larger ventricles of the brain. The posterior ventricle is in the medulla of the hindbrain where the vertebral canal enlarges to form the fourth ventricle. Proceeding anteriorly from the fourth ventricle, the central cavity narrows again to form the aqueduct of Sylvius, which extends to the midbrain region; here it forms the third ventricle. Anterior to the third ventricle, the brain cavity divides into a pair of lateral ventricles which extend into and throughout the length of the cerebral hemispheres. (Fig. 135*B*.)

It is thus evident that the central canal of the spinal cord together with the ventricles of the brain form a continuous central cavity throughout the length of the central nervous system. The vertebral canal of the spinal cord is very small and apparently without definite function, but the brain ventricles serve an important function in the collection and distribution of the cerebrospinal fluid which fills the central cavities and surrounds the entire central nervous system, thus affording protection from mechanical shocks and also as a medium from which nutrient materials are obtained for the neurons.

Meninges.—In considering the cerebrospinal fluid, attention must be given to the three membranes (meninges) that enclose the central nervous system. The outermost membrane (dura mater) completely lines the bony tissue of the skull and, to a lesser degree, the vertebral column. The middle meninges is the arachnoid, and within it is the innermost one, the pia mater, lying in close contact with the nerve tissues of the brain and cord; in fact, the pia mater follows the convoluted surface of the cerebral cortex, while the arachnoid stretches across from "peak to peak" of the sulci. Between the arachnoid and pia mater is the subarachnoid space filled with cerebrospinal fluid.

The latter thus forms a liquid layer completely surrounding the central nervous system.

The cerebrospinal fluid is a product of the blood and is received from the vascular system through thin-walled, high-vascularized areas (choroid plexuses) present in the walls of the brain ventricles, particularly in the lateral ventricles of the cerebral hemispheres. From the lateral ventricle of each hemisphere, the cerebrospinal fluid flows posteriorly, passing through the third, and finally reaching the fourth ventricle. Here it slowly flows through three tiny openings in the thin ventricular covering and then into the extended spaces of the subarachnoid cavity. The route of the cerebrospinal fluid in returning to the blood stream has not been fully determined. The pia mater serves not only as an intimate membranous covering of the central nervous system but also as a highly vascularized tissue in which the blood vessels supplying the nerve elements of the cord and brain have their origin.

FUNCTIONAL FEATURES ASSOCIATED WITH THE NERVOUS SYSTEM

From the functional standpoint, the human nervous system is primarily receptive, conductive, and integrative. We have seen that the function of reception is localized in the many and varied types of peripheral sense organ, capable of receiving the continuous and multitudinous internal and external stimuli. Conduction of nerve impulses is usually regarded as being primarily the function of the peripheral nerve fibers, and rightly so. It must be remembered, however, that the nerve fibers are not independent elements of the nervous system but merely the processes of the neurons located either in the central nervous system or in near-by ganglia. Furthermore, conduction is also an essential function of the fiber tracts extending through the brain and spinal cord. The function of integration, which involves the coordination of all the body structures so as to unify the entire organism, is of paramount importance and is exclusively a function of the central nervous system. Ramifications of the integration function involve the higher functions of intelligence, consciousness, memory, volition, and sensation. Consideration may now be given to these primary functions of the nervous system—reception, conduction, and integration—in the order named.

Reception

Concerned with the reception of stimuli are two groups of receptors, namely, those specialized for external stimuli, which comprise the exteroceptive system, and those influenced by the stimuli arising

internally, which comprise the interoceptive and proprioceptive systems. The receptors of the exteroceptive system are located near the body surface where they are in a position to be stimulated by the various environmental stimuli that impinge upon them, whereas the receptors of the other two sensory systems are located at strategic points throughout the body where they receive the internal stimuli and thus furnish information relative to the condition of the various tissues and organs and of the needs of the body as a whole.

It is at once apparent that the so-called primary senses of the body, namely, touch, taste, smell, temperature, sight, and hearing, are all components of the exteroceptive system with the receptors located peripherally where they are influenced by the particular types of external stimulus for which they are adapted. Furthermore these receptors may be divided into those equipped to receive stimuli from a distance, as in hearing and seeing in which the incoming sound and light waves reach the sensory tissues from varying distances, and into the receptors which are stimulated only by actual contact with certain substances, as in touch, taste, and smell. It might be thought that the olfactory receptors belonged to the distance receptors; but as a matter of fact, the olfactory epithelium is stimulated only when tiny particles of a volatile material are brought into actual contact with the olfactory cells. It appears probable that the sensation of pain arises from specialized sensory cells which are more or less widely distributed among the various types of receptors and are affected whenever a particular stimulus reaches excessive strength. Adequate consideration has been given to the exteroceptive sense organs in the first section of the previous chapter (page 218), but the interoceptive system remains for brief discussion at this time.

The receptors of the interoceptive system are associated with less generally recognized sensations, notably hunger, thirst, equilibrium, and one that may be referred to as the muscle sense. The receptors associated with equilibrium and muscle sense are conveniently grouped as the proprioceptors. There seems to be no reason to regard the interoceptive receptors as essentially different in nature from those responsible for the reception of external stimuli. However, it is clear that the structural elements of the interoceptive receptors are very simple compared with those of the exteroceptive receptors in which, in most cases, the stimuli are first received by highly specialized sensory cells, as in the retina, and then released to the afferent sensory fibers for transmission to the central nervous system. An examination of the visceral, muscular, and supporting elements of the body does not reveal the presence of definite sense organs with sensory cells, and

so it is evident that the internal stimuli are directly received by the dendrites of the sensory nerve fibers at their highly developed terminal arborizations. The latter are abundantly distributed and in intimate contact with the various body tissues. In the voluntary muscles and skeletal elements of the body the sensory fibers are elements of the spinal nerves, but throughout the viscera of the body, in which involuntary muscle tissue forms the effector units, the sensory fibers are associated with the autonomic system. The three basic interoceptive sensations of hunger, thirst, and proprioception may now be considered.

Hunger.—The sensation of hunger appears to be due primarily to involuntary muscular contractions in the wall of the stomach in the absence of the normal intake of food. As the result of the hunger contractions the sensory nerve fibers in the stomach tissues are stimulated, and a discharge of sensory impulses reaching the central nervous system causes a distinctly unpleasant, even painful, sensation which is interpreted as a demand by the nutritive tissues for food. However, the sensation of hunger appears to arise primarily from an empty stomach, which incites a distinct type of muscular contraction, rather than from an actual demand from the tissues for nutritive materials. Thus, when one fasts for several days, it is found that the hunger sensations disappear after a time. If they were primarily associated with the body tissues, it would be expected that the sensations would increase with the continued failure to supply additional nutritive materials. It seems evident also that the unpleasant hunger sensation is not directly associated with the distinctly pleasant mental phenomenon which we term *appetite*. The latter involves the memory of pleasant tastes, odors, and companionship around the festive board and seems to be linked up with a general feeling of well-being. There is, however, an indirect connection between hunger and appetite in that the sight or smell of food, when one is hungry, will incite various activities associated with eating, such as a flow from the salivary glands, whereas, if one is surfeited with food, the presence of additional food brings no response.

Thirst.—It has been shown, in an earlier chapter, how necessary water is to animal metabolism. Any failure of the water supply so that the fluid reserves in the tissues begin to decrease results in a very definite and early warning, the sensation of thirst. This sensation apparently is not localized in the stomach but in the pharynx. Accordingly, the intake of dry or salty food or hot dry air very quickly results in a dry feeling in the throat, which is immediately associated with the sensation of thirst. At first, the thirst sensation is only a gentle warning which may be satisfied with a slight amount of water. When,

however, the supply of water is lacking for a longer time, the demand is increasingly insistent and soon becomes one of the most powerful and painful of all the sensations, with all the sensory elements of the body gradually stimulated by the demands of the tissues for water.

Proprioception.—Proprioception is primarily concerned with coordinated control of voluntary muscles and with the muscular sense that makes one aware of the position of a particular muscle or group of muscles, as in the leg or arm, without looking at them. When the proprioceptive apparatus is destroyed in any region, sensation is lost. The sensory impulses arising in the proprioceptors originate in specific dendritic arborizations of the sensory fibers, abundantly distributed through the voluntary muscle tissues and, also, in the attached tendons. Also bound up in the complicated proprioceptive association is the function of equilibrium which has its primary interpretive area in the cerebellum of the hindbrain. The cerebellum also receives by way of the auditory nerve the afferent impulses originating in the sensory cells of the semicircular canals, which, as we have seen, are the organs of equilibration. The exact role of the cerebellum in maintaining equilibrium is difficult to determine with exactness, but that it is of prime importance is established by the fact that the complete or partial destruction of the cerebellum decidedly mars not only the normal picture of equilibrium but also the essential integrated operation of practically all types of voluntary muscle movement. Again, the maintenance of normal muscle tonus is also bound up in the proprioceptive phenomena. On the whole, the cerebellum apparently should be regarded as the general interpretive center of the afferent impulses from the proprioceptors and the organs of equilibrium. Out of the complete picture thus obtained by the cerebellum, suitable efferent impulses are released which govern tonus, equilibrium, and coordinated voluntary movements, particularly those associated with locomotion and other complex movements that have been gradually learned.

Conduction

From the external and internal receptors of the body, scattered far and wide, widely variable in design and almost innumerable, sensory impulses are continuously being received and conducted over the afferent nerve fibers to the central nervous system, and, from the latter, efferent impulses are released for transmission over the motor and autonomic nerves to the effector units of muscle and glandular tissue. And, as we have already seen, the central nervous system contains important fiber tracts over which countless nerve impulses continuously pass from one end to the other. It is apparent that in the

absence of conduction the receptive and integrative functions would be without effect. The underlying phenomena responsible for the conduction of nerve impulses are, to a considerable extent, bound up with secrets of the living state which, as yet, are undisclosed. Nevertheless numerous important facts pertaining to conduction, which were established by years of research, are now recorded, and a few of the most important of these may now be considered.

In the first place, the conduction of impulses over the nerve fiber is unqestionably a vital process in which oxygen is used, carbon dioxide is released, and a slight rise in temperature occurs, as in other cellular activities. Accordingly, conduction must be basically a process in which potential chemical energy present in the protoplasmic compounds of the neurons concerned is released by oxidation. The chemical changes associated with the movement of a nerve impulse along the fiber has been compared to the burning of the explosive in a fuse as it proceeds in regular fashion from the lighted end. However, it is certain that, when the explosive compound has undergone the chemical changes associated with combustion, the original substance cannot automatically be restored; whereas the chemical changes in the cytoplasm of a nerve fiber, when the impulse is transmitted, are only temporary, so that another impulse may be transmitted almost immediately.

It has long been established that the conduction of nerve impulses is accompanied by electrical phenomena. This can be shown by placing the electrodes of a galvanometer of the proper sensitivity in contact with an active living nerve fiber and, then, artificially stimulating the latter at some point beyond the electrodes so that nerve impulses will pass along the fiber. When the advancing impulse reaches the first electrode, an electric current, known as the *action current*, will be registered moving toward this spot from the second electrode. As the impulse passes to the portion of the nerve lying between the two electrodes, no current is detected; but when the impulse reaches the point of the nerve where the second electrode is attached, a current is detected flowing from the region of the first electrode toward the second; that is, the direction of the current is the reverse of that first indicated. Since the action current flows toward the region of the fiber over which the impulse is passing, it is evident that the latter temporarily reduces the electric potential of successive points of the fiber (that is, they become negative) as it moves along. If no impulse is passing over the fiber, the galvanometer shows an absence of current, which, of course, means that all regions of the fiber have the same electric potential. The action current is distinct from the nerve impulse

but is induced by the conduction of the latter along the fiber. (Fig. 141*A*, *B*.)

In the earlier chapter dealing with the Muscular System, a description was given of the muscle-nerve preparation in which a voluntary muscle and the attached nerve were removed from an experimental animal and used for the study of muscle contraction (page 179). Such a preparation is also of great value, as was there indicated, for the study of conduction in nerve fibers. It is possible, in the first place, to ascertain the effects on nerve fibers of various types of stimulus, such as electrical, thermal, chemical, and mechanical, all of which will stimulate nerve tissue and produce nerve impulses. In general,

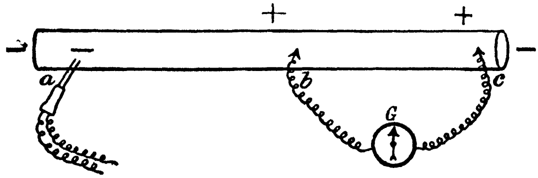


FIG. 141*A*.—Illustrating electrical phenomena associated with the passage of a nerve impulse, as described on page 272. *a*, electrodes for applying stimulus to nerve; *b*, *c*, electrodes connecting with galvanometer *G*. (*Howell, "Physiology," W. B. Saunders Company.*)

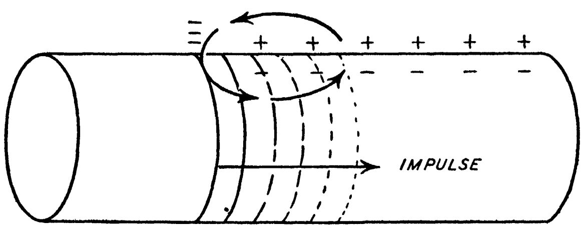


FIG. 141*B*.—Schematic diagram illustrating the changes in the electric potential during the passage of a nerve impulse. (*Buchanan, "Elements of Biology," Harper & Brothers. Slightly modified after Gerard.*)

it has been found that the electric current offers the best type of artificial stimulus, since it can be controlled accurately with respect to the area of stimulation, the strength of stimulus, and the time during which it acts. It should be noted that the *continuous* flow of an electric current through a nerve does not stimulate it unless the current is of considerable strength, in which case it is probably injurious to the nerve tissue. On the other hand, nerves are readily stimulated by *interruptions* in the flow of an electric current. Thus nerve stimulation occurs at the instant when the switch is closed and the electric current begins to flow (make-shock) and again when the flow of the current is stopped by opening the switch (break-shock). The physiologist using the proper electrical stimuli can study the nature and characteristics

of the artificially incited nerve impulses, both in excised nerves and also in those in their normal location in the body. In the latter case, electrodes placed on the skin may be used to stimulate particular nerves and muscles. (Figs. 91, 92.)

Speed of Nerve Impulse.—Experimental studies on nerve conduction show that the speed of the impulse is subject to wide variation. In the first place, the rate is much slower in a cold-blooded animal, like the frog, than it is in a warm-blooded organism. Thus the maximum speed of the nerve impulse in the frog is in the neighborhood of 140 ft. per second, while in man the impulse may attain a speed more than twice as rapid, or almost 300 ft. per second. Other experiments have shown that the conduction of the nerve impulse under identical conditions is more rapid in myelinated than in nonmyelinated nerves and that the rate also varies in accordance with the size of the nerve; in the larger nerves, with the correspondingly greater number of nerve fibers, the impulse is conducted more rapidly than in the smaller ones. The figure, given just above, is for conduction in a large medullated nerve. The measurements taken on small nonmyelinated nerves show an impulse rate of less than 5 ft. per second in some cases. Again the speed of the nerve impulse may be progressively reduced by decreasing the temperature of the nerve fiber until, at a point a little above freezing, conduction is entirely stopped. With all conditions equal, no detectable difference exists between the transmission phenomena of the sensory fibers carrying afferent impulses toward the central nervous system and those occurring in the motor fibers in which efferent impulses are conducted toward the peripheral effectors.

In the earlier discussion of muscle function, it was noted that the repeated contraction of a muscle, without adequate rest periods between, involved muscle fatigue which considerably altered and, finally entirely prevented, contraction (page 184). The evidence for fatigue in the nerve fiber following repeated conduction of impulses over considerable periods, even up to several hours, is not clear. In fact, the results obtained by various investigators have shown that a nerve fiber is competent to receive stimulation and to conduct the resulting impulses over long periods. Slight fatigue immediately following conduction, as shown in recent experimental results, possibly decreases conduction somewhat. Apparently protecting the nerve against too rapid onset of conduction is a refractory period following a stimulus, during which a complete loss of excitability occurs and, accordingly, another stimulus cannot be received for conduction. The refractory period lasts from 0.002 to 0.003 second, after which the nerve fiber can again be stimulated. It is evident that the refractory

period, brief as it is, is sufficient to permit the recuperation of the conducting elements in the nerve fiber. The question as to the nature of the activity at the terminal arborization of a nerve fiber, which incites activity in an effector, is a difficult one. How, for example, does the nerve impulse cause a contraction of a muscle fiber? Evidence is accumulating to indicate the presence of a mediating hormonal substance, acetylcholine, presumably secreted by the terminals of the efferent fibers, which brings the effector element into activity (page 495).

Integration

Integration is necessarily the controlling function of the entire body. It has its structural basis in the neurons of the central nervous system and is an exclusive function of this major division. This is unlike the condition noted in connection with the receptive and conductive functions which are shared by both the peripheral and central systems. Integration as applied to the nervous system is a very comprehensive term which includes a number of basic associated functions. Integration may be regarded as a process of internal unification through which all the diverse functional units of the body are caused to work together for the complete unit, the individual. Involved in this master function are the reception and interpretation of the sensory impulses from every area of the body, the selection of the correct routes for the efferent impulses, and the regulation of the effector units associated with all types of movement and secretion so that activity may be initiated, increased, or inhibited as the conditions demand. Thus integration is responsible for the coordinated control of all the diverse elements of the organism. Many of the integrative adjustments do not involve consciousness, which means that they are not referred to the cerebrum, but this function is always ready to be called into play as a part of the integrative phenomena.

Reflex Arcs.—Experimental studies concerned with the analysis of the integrative function in the vertebrate nervous system give evidence that the reflex action is an essential element. Apparently reflex actions are responsible for most, if not all, of the bodily activities. A reflex action may be defined as an involuntary, or unconscious, action occurring in some element of a peripheral effector in response to a stimulus received by a sensory receptor and transmitted to the central nervous system over the afferent nerve fibers. Thus is set up the so-called reflex arc, which, in the simplest type of reflex, might conceivably consist only of the afferent fibers of a sensory neuron carrying the impulse to the spinal cord where synapse is made with the dendrites of a motor neuron. The latter transmits the impulse,

now efferent, to the connected muscle fibers which act in response to the original sensory impulse.

It is doubtful if a reflex arc that involves only two neurons, as just described, is more than a theoretical possibility. Undoubtedly the normal reflex arc is much more complicated and involves, in addition to the arc just described, conduction up and down fiber tracts of the central nervous system and synapses at the proper levels with other neurons, thus bringing into play an integrative action by the central nerve elements. The sensory axon, on reaching the cord, may divide into an ascending fiber and a descending fiber from each of which side branches (collaterals) will be given off that synapse with the motor neurons at various levels. It is thus possible for an impulse entering

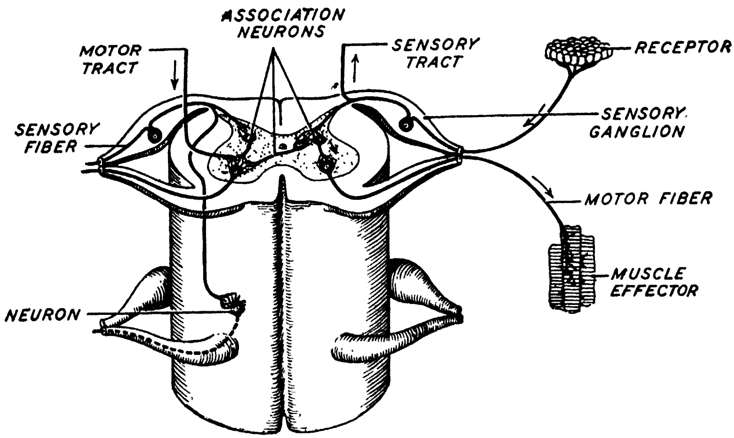


FIG. 142.—Diagram illustrating the components of a reflex arc. (*Buchanan, "Elements of Biology," Harper & Brothers, after Kuhn, redrawn.*)

the cord over a single sensory neuron to reach a considerable number of motor neurons for transmission to various peripheral effectors. (Fig. 142.)

The integrative action of the brain and spinal cord is best seen in a third type of reflex arc, probably the most important of all, in which a third type of neuron is involved, namely, the association (integrative) neurons. These lie wholly within the central nervous system, as previously noted, and mediate between the sensory and motor neurons (page 254). Thus, the incoming sensory impulses are received by the dendrites of the association neurons and conducted by them directly to the proper motor neurons or even to the brain areas for complete integration if complicated reactions are indicated. The latter may possibly involve complete integration of all body units. Consider, for example, the reactions of a surgeon who accidentally pricks his

finger with an infected instrument while operating, in comparison with his reactions when he jabs his finger against the point of his tiepin while dressing. In the latter case, the finger is quickly drawn away by the simple involuntary reflex action, and the pinprick is dismissed with little thought. But the injury received while operating is considered in an entirely different light by the surgeon's nervous system. The sensory impulses not only incite the simple reflex action but are instantly projected to the highest centers of the brain where decisions are made and efferent impulses released which quickly involve all the nervous centers and the associated effectors. There is a unification, an integration, of all the body units in an endeavor to find the best possible solution for the serious problem presented. In this connection, the association areas of the brain are undoubtedly of basic importance in causing the union of all the nerve elements to synthesize the complete concept. The sensory impulses from the injured tissues and the visual impulses from the eye reach the separate localized areas in the cerebral cortex, where they are interpreted. They are brought together through the association fibers. The function of memory is also involved. The surgeon remembers what he has previously learned about the dangers of an injury by an infected instrument. Possibly all the neurons of the entire cortex are instantly brought into the picture, and from them a mental image, or consciousness, arises which is the basis of the efferent impulses released to the effectors.

Reflex actions resulting from internal and external stimuli are continuously occurring throughout life. It is the way in which the organism solves its problems and adapts itself to the environment. A very important question which puzzles the physiologists and psychologists is the determination of the limits of reflex activities in the human organism. Some would say that all our activities, physical and mental, are essentially reflex in nature, differing in degree of complexity but not in their basic nature. Others hold strongly to the belief that, in the higher mental processes involving such phenomena as intelligence, judgment, will, and memory, the nervous functions go beyond the automaticity of the reflex. At all events, except in the highest mental activities, reflex actions involving receptors, afferent conductors, adjustors, efferent conductors, and effectors are highly important in determining the response of the body to stimuli of all kinds.

It has previously been shown that reflexes are of different degrees of complexity in accordance with the number of neuronic areas involved in the reflex arcs. It is also apparent that complex reflex actions involve the neurons in various brain areas or even those of the entire

brain, for in it the adjustments take place that are necessary in bringing about the integrated responses to the stimuli that referred to it. In a general way, it can be stated that the spinal cord is dominant over the peripheral nerve elements, that the neuronic areas of the brain are dominant to those of the spinal cord, and, finally, that the neurons of the cerebral cortex are the chief controlling and integrating units of the nervous system and, therefore, of the entire body. Out of their activities develop the highest function of the nervous system, that of intelligence. The "intelligent" cerebral neurons are able to determine what response is suitable for a given condition and so can inhibit or augment the normal reflex or initiate an independent action as seems best.

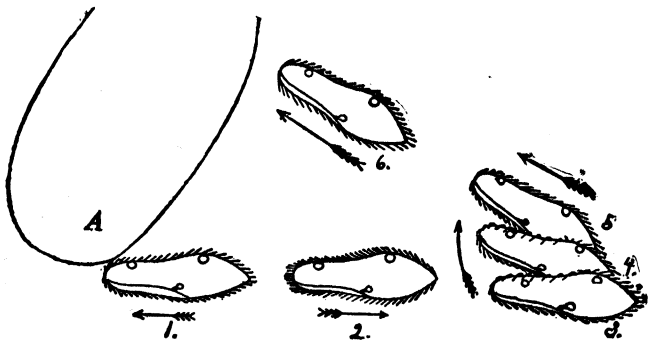


Fig. 143.—Diagrams illustrating the avoiding reaction of Paramecium. At 1, the animal receives stimulation by coming into contact with a solid object *A*. The avoiding reaction is shown in 2 to 6; the direction of movement indicated by arrows. (*Woodruff, after Jennings.*)

As shown above, the automaticity of reflex actions, in general, is noteworthy. They are essentially determined so that a certain stimulus induces predictable response. Bright light invariably causes the pupils of the eye to contract, whereas in dim light they enlarge; and so it goes in many, many instances. This is the field of the tropistic reactions[1] that has received so much attention during recent years. Tropisms are defined as orientations, or directed reactions, in a field of force. Such automatic reflexes, apparently established in the basic pattern of the organism, are termed *unconditioned reflexes* and include the great majority of the reflex actions. (Fig. 143.)

Another group of reflexes, known as *conditioned reflexes*, are acquired individually through training. Their establishment involves consideration by the higher nerve centers of the cerebral cortex just as does anything that is learned. In addition, the conditioned reflex

[1] Consult Appendix: Tropisms.

is built upon the pattern of the inherent unconditioned reflex. The distinctions just stated are well shown with dogs in the secretion of saliva when food is taken into the mouth. Under such conditions, the secretion of saliva is a normal unconditioned reflex. The development of a conditioned reflex, based upon this normal saliva reflex, can be accomplished by subjecting the animal to another stimulus, in this case the ringing of a bell at the time food is given. Thus an association between food and the sound of the bell is gradually built up in

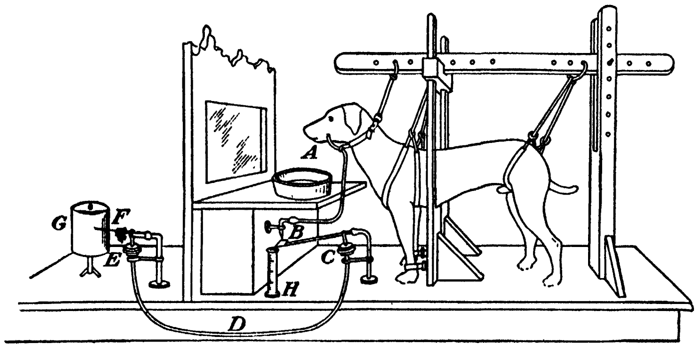


FIG. 144.—Apparatus for developing a conditioned reflex in a dog, as devised by Pavlov. *A*, cannula inserted in the cheek to collect saliva; *B*, metal plate on which drops of saliva fall. When this occurs pressure is exerted through the tambour (*C*) on column of air in tube (*D*). This exerts pressure upon another tambour (*E*) which carries the writing lever (*F*) which is arranged to make a record on the smoked paper of the kymograph, indicating the flow of saliva. *H*, glass graduate for measuring the quantity of saliva. (*Watkeys, Berry, after Yerkes and Morgulis.*)

the cortex after some 30 to 40 feedings. When this association is reached, a reflex flow of saliva will occur at the sound of the bell and in the absence of food. This is the conditioned reflex. It is not a permanent reaction; its continuance depends upon receiving food when the bell rings. If the auditory stimulus is repeated several times unaccompanied by food, the conditioned reflex with secretion of saliva will gradually disappear. Then, the animal returns to the original unconditioned reflex pattern which is responsible for the secretion of saliva when food is received. (Fig. 144.)

PLATE XV.—The allegorical title page from *De generatione animalium*, one of the last publications of William Harvey, who discovered the circulation of the blood. This work was published in 1651, six years before Harvey's death. Jove sits enthroned with his eagle and is releasing various animals, all of which come from the egg—*Ex ovo omnia*. (*Redrawn by L. Krause.*)

CHAPTER XII

THE BIOLOGY OF GROWTH AND REPRODUCTION (I)

The material presented so far in this volume has been concerned with the structural and functional features of the various major organ systems that make up the human body and by which the life processes are continuously maintained. But, in addition, each individual is also supplied with a reproductive mechanism which is not concerned with the maintenance of the life functions in the individual but with the continued propagation of a particular type of organism, the species, through the production of new individuals. Thus, from the standpoint of the species, the reproductive system is essential, but, from the standpoint of the individual, it is not essential. However, it is the perpetuation of the species that carries the great weight in nature, and so we find that the process of reproduction is dominant in many organisms, far transcending all other functions in structural and functional development. Furthermore, it should be noted that reproduction is a unique characteristic of protoplasm. It is difficult to conceive of living matter lacking the power of reproduction, and, on the other hand, it is just as difficult to conceive of any type of nonliving material that could possibly possess this amazing life function.

To the biologist, reproduction is seen as a process primarily based upon the power of growth and cell division. This was indicated in the opening chapter where it was shown that the growth of cells results from the dominance of the constructive metabolic processes and that, when the cell has grown to a certain characteristic size, it divides to form two daughter cells. The latter, under favorable conditions, increase in size until they equal that of the parent cell. It was also shown that, basically, cell division is reproduction. This fact is clearly evident in the unicellular forms of plants and animals in which the division (binary fission) of the one-celled body produces two independent daughter individuals. In the multicellular organisms, however, the relation between reproduction and cell division is obscured by the fact that cell division normally results in adding additional cells to the body of the individual rather than in the formation of additional individuals. Eventually, however, when the proper stage of development has been reached, new individuals are produced

by cell division occurring in a particular region of the multicellular parent individual or by a particular kind of cell division resulting in the production of the highly specialized gametes, eggs and sperm.

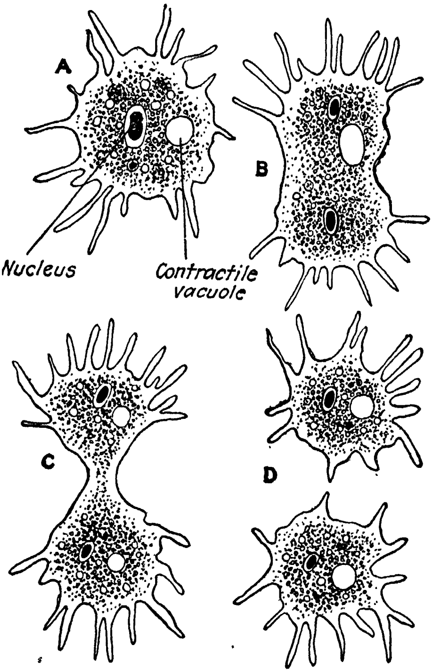


FIG. 145.—Asexual reproduction by cell division (binary fission) in Amoeba. (*Wolcott, modified after Schulze.*)

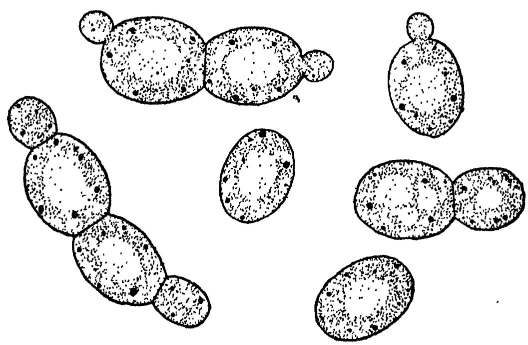


FIG. 146.—Asexual reproduction in unicellular yeast plant by budding. When buds remain attached, temporary colonies are formed. × 1,500. (*Haupt.*)

It will be well to leave the consideration of the important features associated with cell division until the next chapter and continue here with the general consideration of reproduction. (Fig. 145.)

TYPES OF REPRODUCTION

In the first place, it should be noted that reproduction is either asexual or sexual. The basic difference between these two methods is uniparental or biparental inheritance, or, in other words, whether the offspring have one parent or two parents. In asexual reproduction, the offspring are formed by the growth and division of cells from one parent. In sexual reproduction, two types of individuals are concerned, male and female, in reproduction, and each new individual is formed following the union of two gametes: the male sperm and the female egg. This constitutes fertilization and produces a biparental fertilized egg, or zygote, which divides repeatedly and gradually attains parental size.

Asexual Reproduction

As an example of asexual reproduction in the multicellular organism, consideration may be given to the process of budding, which is characterized by the rapid growth and division of the cells in certain regions of the parental organism with the consequent formation of a new individual, attached at first to the body of the parent but, in time, separating as an independent organism. Budding is an established method of reproduction even in unicellular organisms, as in the classic example of the yeast cell where a tiny area of the cytoplasm of the spherical parental cell enlarges to form a knob-like protuberance which later separates as an independent daughter cell. In the multicellular animals, common examples of budding are found in Hydra and other Coelenterates. The buds in Hydra are formed in various regions in the wall of the tubular body and gradually develop from a minute group of cells to multicellular structures almost as large as the parent Hydra before they finally separate. (Figs. 146, 147.)

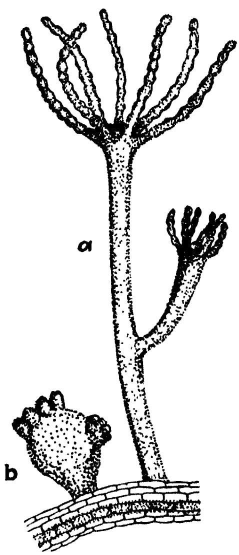


Fig. 147.—Asexual reproduction by budding in the primitive metazoan, Hydra. Bud is seen at the right of the parent animal. *a*, expanded; *b*, contracted. × 12. (*Wolcott.*)

Closely related to asexual reproduction by budding is asexual reproduction through the regenerative process. Thus, in many organisms, it is possible to divide the body into several pieces and have each piece gradually grow into a complete organism. This process is very familiar in the plant world where standard methods of propaga-

tion involve the cultivation of cuttings from the parent plant, as in various common house plants or, in the fields, as in the potato or sugar cane. But many examples of reproduction through regeneration exist also in the animal kingdom. Again one of the best examples is found in Hydra, but representatives of various higher groups, particularly the worms, also exhibit great regenerative abilities. Thus in the marine flatworm, *Lineus socialis*, it has been shown that pieces with a calculated volume only 1/200,000 of the normal size may regenerate a complete individual. In this and many other instances it is apparent that regeneration is equivalent to asexual reproduction. (Fig. 148.)

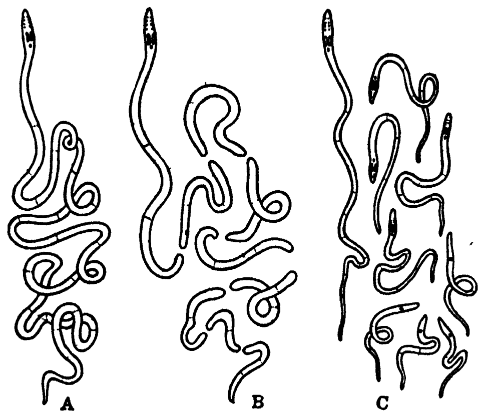


Fig. 148.—Asexual reproduction in a marine flatworm (*Lineus socialis*) by fission. *A*, mature worm; *B*, division into nine parts, each of which, as shown in *C*, regenerates to form a normal worm which soon attains full size. (*Woodruff, after Coe.*)

Speaking generally, it may be said that the power of regeneration in the animal kingdom becomes increasingly limited in the higher types and finally reaches a condition, as in man, in which very little regeneration of the highly developed tissue and organs is possible. To the biologist, it is apparent that restriction of regeneration is directly associated with the increased tissue differentiation that is characteristic of the higher animal types. That is to say, the greater the differentiation in an organism the less the ability to regenerate missing portions. In such cases, as will be seen later, when injury occurs, unless the functioning of essential organs is disturbed, the continuity of the tissues is reestablished by the development of a connective, or scar, tissue which repairs the wound area but does not have the functional or structural characteristics of the tissues it replaces. Thus repair but not regeneration takes place. Differentiation becomes increasingly manifest during embryonic development as the ultimate adult condition gradually proceeds out of the relatively

undifferentiated embryonic condition. But this is a subject that may be well left for more detailed consideration when the embryological processes are studied.

Binary fission, budding, and regeneration, as discussed in the paragraphs just above, are purely asexual in nature and, in addition, are not dependent upon the development of specialized reproductive cells of any type. There are two other well-known methods of asexual reproduction, however, namely, spore formation and parthenogenesis, which involve the formation of special reproductive cells. These are worthy of some attention because of their widespread use in the living world. In the case of spore formation, the organism at some period or periods in its life history typically produces enormous num-

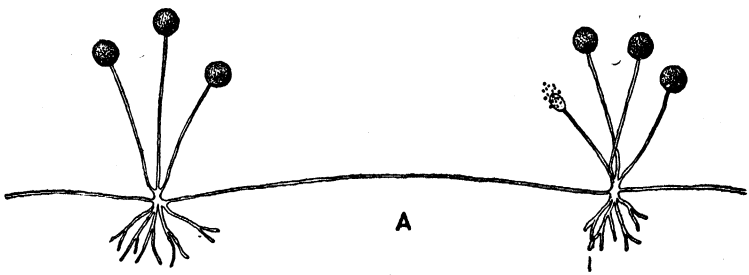


FIG. 149.—A common bread mold (*Rhizopus nigricans*): horizontal branch with two groups of erect spore-bearing branches (hyphae). One of the spore cases is discharging spores. × 15. (*Haupt.*)

bers of microscopic cellular bodies, or spores, each of which is capable, when given the proper conditions, of developing into an independent fully formed individual. Typically, spores are provided with coverings of a particular type which make these reproductive cells very resistant to unfavorable environmental conditions, and so they are ideal for wide dissemination and later development when the conditions become favorable. (Fig. 149.)

Spore formation in the plant kingdom is of almost universal occurrence. In all the higher plant types, asexual spore formation is linked with sexual reproduction in the complete life cycle, the latter consisting of an asexual spore-forming generation which alternates with the sexual gamete-producing generation. Thus, the spores produce the sexual generation, whereas the zygote, formed by the fusion of the male and female gametes, gradually develops into the spore-producing generation. This constitutes alternation of generations which, though not of universal occurrence, is extraordinarily widespread in the plant kingdom. Furthermore, alternating sexual and asexual generations are not uncommon in the lower animal groups. Spore formation, in

the animal kingdom, appears to be segregated in an important class of unicellular animals, the Sporozoa, which are of major importance as disease-producing parasites. Spore formation in this class is typically associated with complex life cycles in which sexual phenomena are involved. (Figs. 150, 250.)

Finally, asexual reproduction may occur through the parthenogenetic development of the female gamete, or egg. Examples of parthenogenesis have long been recognized as occurring normally in nature, particularly in representatives of the great insect group. The parthenogenetic development of the male bee, or drone, (page 448) is the best known example and, in fact, has long stood as a classic instance of natural parthenogenesis. As a result of biological experimentation on

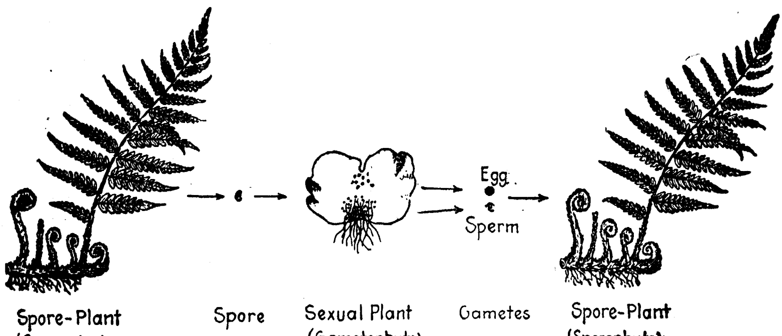


FIG. 150.—Alternation of sexual and asexual generations in a fern. (*Sinnott.*)

the eggs of various animals, several examples of artificial parthenogenesis have been discovered, beginning with the original work of J. Loeb on the Echinoderm egg some 40 years ago. This experimenter found that it was possible to incite the eggs of the sea urchin to develop in the absence of sperm if the proper chemical stimulants were used. In later years, the original results of Loeb have been greatly extended, so it is now established that various types of egg will begin to develop under the influence of artificial stimuli, even including those of highly developed vertebrates, like the frog or rabbit.[1]

SEXUAL REPRODUCTION

Thus far our discussion of reproduction has been confined to asexual reproduction in which the new individual arises by the cellular activity of one parent, that is, uniparental inheritance. But reproduction is

[1] The production of mature rabbits from eggs induced to develop through artificial parthenogenesis was announced by Dr. Gregory Pincus in the *Proceedings of the National Academy of Sciences*, November, 1939.

otherwise in the higher animals, for asexual reproduction has been replaced by sexual reproduction, and each new individual is accordingly supplied with a legacy of materials from the two parents, the condition of biparental inheritance. The basic difference between the male parent and the female parent lies in the production of a characteristic type of reproductive cell, or gamete, the sperm or the egg. The gametes are usually produced in great numbers by both sexes but more particularly in the male. Underlying gamete formation, just as in any type of cell, are the basic processes of growth, cell division, and differentiation.

It should not be thought that sexual reproduction is entirely confined to the higher plants and animals, for numerous instances of it are found in the unicellular organisms. In the simplest examples, fusion occurs between two cells, or gametes, of equal size and uniform structural characteristics (isogamy), but, even in the lowest groups of living organisms, examples may be found in which the male and female gametes are as clearly differentiated as in the higher organisms. Accordingly, in fertilization, fusion occurs between a free-swimming sperm and a passive egg cell of more or less typical cellular pattern (anisogamy). Differentiation of the gametes, for example, is very apparent in the unicellular sporozoon, *Plasmodium vivax*, which is responsible for malaria, one of the most dangerous of the human diseases. In Plasmodium, sexual reproduction takes place in the body of the mosquito. The male and female gametes formed by this sporozoon give every indication of as great differentiation as those of higher types. Thus it is clear that, from the lowest animal groups up to the highest, sexual reproduction stands as a well-established phenomenon, but sexuality is of increasing importance in the higher animal types and in the vertebrates constitutes the only normal method of reproduction. In the plant kingdom, on the other hand, asexual reproduction by spore formation and by regeneration remains dominant in all groups. (Figs. 151, 250).

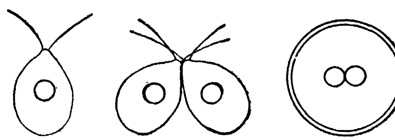


FIG. 151.—Successive stages in the fusion of two equal-sized cells (isogamy) of the unicellular algae, *Chlamydomonas*: the basis of sexual reproduction. (*Watkeys, Stern.*)

Also the hermaphroditic condition, as in the earthworm, in which the same individual bears gonads for the production of both male and female gametes, disappears with the advent of the vertebrate. Numerous examples of alternation of generations and also of hermaphroditism are well-known in even the highest invertebrate groups.

Another interesting variation of sexual reproduction, particularly prominent in the great molluscan group, is the reversal of sex which occurs in the life cycle of each individual. Thus the organism matures first as a male, later changes to a female capable of producing female gametes. Reversal of sex does not occur normally in vertebrate animals, but an authentic instance is recorded in which a normal egg-laying hen changed to a rooster producing fertile sperm. The reversal of sex in this instance was due to the destruction of the ovarian tissues following a tubercular infection. This raises the question that has received great attention in the last quarter of a century, namely, the

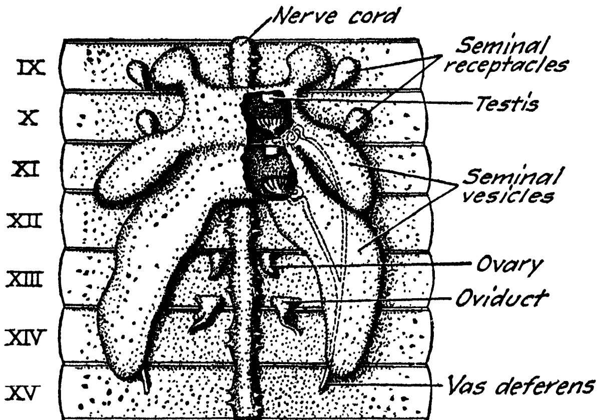


Fig. 152.—Diagram illustrating male and female reproductive organs in the earthworm, a hermaphroditic organism. They lie near the anterior end, segments IX to XV as indicated. (*Wolcott, after Wieman.*)

effect of the gonadal endocrine secretions in altering the sexual characteristics of the individual. Some consideration has already been given to this in the previous chapter on Secretion (page 115). (Figs. 152, 153.)

Due to the fact that, as indicated above, reproduction in the vertebrates is exclusively sexual and, furthermore, that the sperm and eggs are always produced in separate individuals, the variable features of vertebrate reproduction are largely associated with the mechanics of fertilization and development of the zygote. The essential feature of fertilization is always the actual union, or *amphimixis*, of the chromatin materials present in the sperm nucleus with the chromatin carried in the egg nucleus. Thus fertilization, since it involves amphimixis, makes biparental inheritance possible; the nuclear contribution from each parent uniting to form a common nucleus, or *synkaryon*, in the fertilized egg, and each parent making equal contribution to the

characteristics of the new individual. The fertilization of the vertebrate egg may occur externally or internally. External fertilization, that is, outside the body of the female, is, however, the more common and primitive method in the water-living forms. In such types, both the eggs and sperm are adapted for temporary survival and union in a water environment. Since the gametes of the two sexes ripen at the same time and tremendous numbers of them are usually discharged in fairly close proximity to each other, the chances are that the actively swimming sperm will come into contact with the eggs, thus bringing

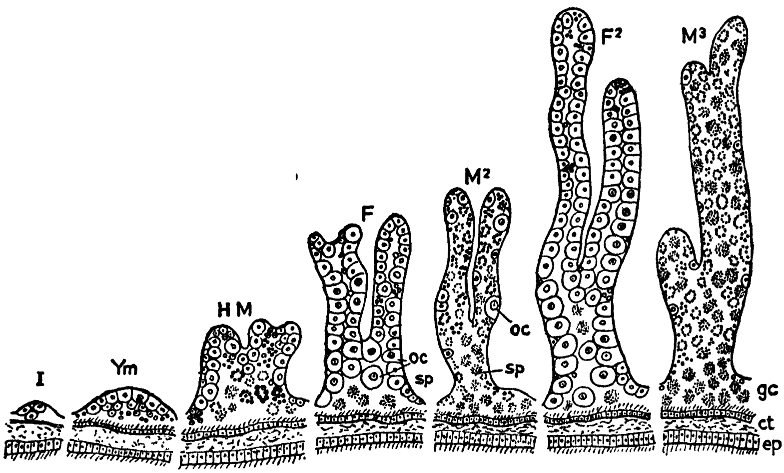


FIG. 153.—Schematic diagram illustrating the sequence of changes in the gonads of an oyster during sex reversal. *oc*, oocytes (large cells); *sp*, male cells (small dots); *I*, gonad without sex differentiation; *Ym*, gonad of young animal, bisexual; *HM*, male phase but somewhat hermaphroditic; (M^2, M^3) later stages in the development of the male gonad; *F*, first female phase; later female stage shown in F^2; *F*, M^2, F^2, M^3, successive stages in sex reversal; *ct*, connective tissue; *ep*, epithelium; *gc*, genital gland. (*Shull, after Coe.*)

about fertilization and embryonic development. With external fertilization and development, the reproductive responsibilities of the parents cease with the formation and liberation of the gametes. In certain instances, notably in the frog, though fertilization and development are external as indicated, a temporary pairing (amplexus) of the male and female frogs occurs at the time the eggs and sperm are discharged, which insures a very high percentage of fertilization. (Fig. 154.)

Numerous examples of animals are found, with both water and land habitats, in which internal fertilization of the eggs occurs, but the ensuing embryonic development is external, for the fertilized eggs leave the body of the mother shortly after fertilization and continue

their development externally. In the warm-blooded birds, it is necessary to supply the developing eggs with the proper body temperature, or incubate them, in order for development to continue after the eggs are laid. Internal fertilization always requires the pairing, or copulation, of the parents, during which process the transfer of sperm from the male to the female takes place. Also, internal fertilization requires the development of external male genital organs for the transference of the sperm to the female, as well as the elaboration of the female organs concerned with the reception and conduction of the sperm to the eggs. In some animals, exemplified by the queen bee, storage of sperm is an important function accomplished by the presence of special sperm receptacles.

In the mammalian female, the reproductive mechanism is further complicated by the retention of the fertilized egg in a special cavity, the uterus or womb, modeled out of a portion of the egg tubes, or oviducts, through which the eggs pass on their way to the exterior. The proper care and nourishment for the embryo developing in the uterus present a number of difficult problems, the solutions for which have been found through the formation of a combination fetal and maternal structure, the placenta, which is described below.

It is evident to the biologist that the underlying factor primarily responsible for variation in the development of the vertebrate egg lies in providing adequate nutrition for the embryo. The eggs of various vertebrates show great variation in the amount of nutritive materials or yolk that they contain at the time of fertilization. The embryo that develops from a type of egg in which very little reserve food is stored must necessarily be provided with some method for quickly securing nourishment from the environment. An example of this may be noted in the embryos of the lowly starfish which, lacking reserve food in the eggs, are able to form a primitive nutritive system for securing and utilizing outside nutritive materials a few hours after fertilization. With the exception of the mammals, the eggs of the vertebrates are heavily yolked, and, accordingly, the embryo is able to develop for a considerable period without the necessity of seeking food supplies from the surrounding environment.

Food storage reaches a high peak in the hen's egg and those of other birds. This condition makes it possible for the developing embryo to remain sealed up in the original eggshell for the entire incubation period of three weeks, at the conclusion of which it breaks through the shell, or hatches, as a well-developed active individual. On the other hand, the mammalian egg is practically free from stored food but gives evidence during its development, as will be shown later, of being

closely related to the heavily yolked eggs of the birds and reptiles. The lack of stored food in the mammalian egg makes it necessary for the zygote to secure nourishment from outside sources very quickly, and this is accomplished by the rapid development of an outer layer of nutritive cells, the trophoblast, which has the ability to secure the essential food materials from the tiny area in the maternal uterine walls in which the microscopic embryo is embedded.

But the amount of stored yolk not only governs the nutritive requirements of the embryo; it also varies the pattern of early development with respect to the numbers and arrangements of the cells formed by the successive divisions of the zygote. For the stored yolk is inert, nonliving material, and its presence in the egg in any considerable amount retards cell division and considerably modifies the early embryonic stages. Thus we find that eggs with a comparatively small amount of yolk evenly distributed through the cytoplasm (homolecithal eggs) exhibit a total cleavage (holoblastic cleavage) marked by the formation of daughter cells which are fairly uniform in size.

Eggs containing a considerable amount of yolk show a tendency for the nutritive materials to be concentrated at one pole (nutritive or vegetal pole) and to leave the cytoplasm of the animal pole relatively free. Eggs of this latter type are known as *telolecithal eggs*. When the mass of yolk is not too large, as is the case in the frog's egg described below, the cleavage is holoblastic just as noted in the homolecithal eggs, but a distinct lag occurs in the cleavage planes when they pass through the yolked area of the vegetal pole; this tends to result in the formation of unequal-sized cells. Finally, in eggs with a very large amount of yolk, as in the hen's egg, the vegetal pole is greatly enlarged; the animal pole comparatively small. The cleavage is partial, or meroblastic, and entirely confined to the animal pole. It will be unnecessary to consider cleavage types further at present, for in the following description of vertebrate reproduction, as shown in the frog, bird, and man, the various important differences will be indicated.

DEVELOPMENT OF THE FROG

A close relationship exists between the excretory and reproductive systems in the vertebrate organism. This fact is seen to particular advantage in the urogenital system of the male frog in which the paired testes lie in close association with the kidneys. In fact, the testes and kidneys are directly connected by numerous fine ducts, the vasa efferentia, which convey the ripened sperm from each testis. On leaving the testis, these sperm ducts pass directly into the kidney tis-

sues where they connect with the ducts leading to the urogenital canals. The latter extend from the kidneys to the cloaca and thence to the exterior. And so the urogenital canals, as the name indicates, serve as common ducts for the passage of urine from the kidneys and sperm from the testes. (Fig. 154.)

Male.—The testes in the frog are seen in gross structure as yellowy-white, capsule-shaped bodies, about ¼ in. in length, situated on the ventral side and near the anterior end of each kidney. Projecting anteriorly from each testis is the so-called fat body with numerous

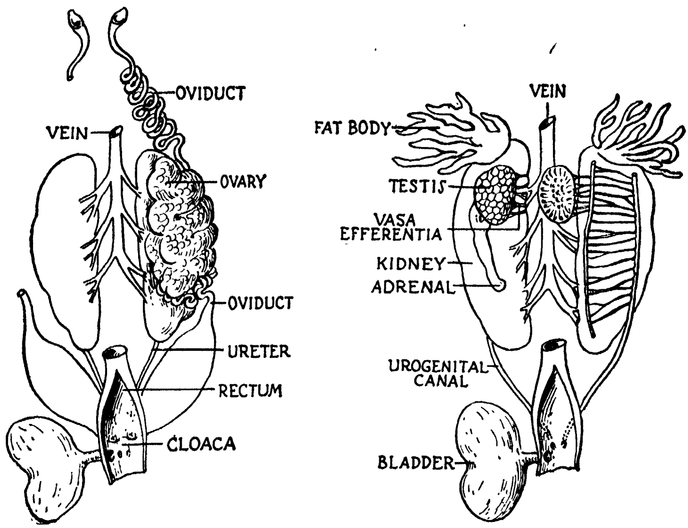


Fig. 154.—Urogenital systems of the male (right) and female (left) frog. In the female only one ovary and oviduct are shown. In the male the testis and kidney at the right have been opened to show the course of the vasa efferentia through the kidney. (*Redrawn by L. Krause from Shull. Modified.*)

tubular branches projecting in various directions. The fat bodies are not directly concerned with the reproductive processes but serve as storehouses for excess nutriment which later can be utilized by the body tissues as needed, chiefly, perhaps, in germ cell formation. Passing now to the histology of the testis, a microscopic examination of sectioned material shows that it consists of a mass of very fine, coiled tubules, intermingled with abundant blood, nervous, and connective tissue elements. These are the essential seminiferous tubules in which great numbers of the sperm develop. They have their origin in the primordial germ cells present in the walls of the tubules.

Female.—Turning now to a consideration of the female reproductive organs of the frog, which may also be regarded as fairly representative of the vertebrates in general, they will be found to consist of a

pair of egg-producing gonads, or ovaries; a closely associated pair of fat bodies very similar to those already noted in the male; and, finally, a pair of oviducts which carry the eggs from the ovaries to the cloaca. The frog ovary is essentially a sac-like structure with a fluid-filled central area. The innermost layer of the covering tissues constitutes the germinal epithelium in which the undeveloped germ cells, or oögonia, have their origin. As in the testis, these unmatured germ cells conform in general, to the cellular pattern of body cells, and then they pass through a series of developmental stages (oögonia, primary oöcytes, and secondary oöcytes) until the mature egg stage is finally attained. Due to the gradual storing of yolk material, as noted above, the egg cells increase in size until the mature frog's eggs are several times the size of the typical body cells. (Fig. 154.)

The eggs reach their full development in the frog at only one period each year. This is normally in the early spring, at which time the two ovaries, distended with great numbers of the large egg cells, fill most of the space in the abdominal cavity. At the proper stage of maturity, the eggs break directly through the thin ovarian wall in large numbers and are drawn by ciliary action into the opening of the corresponding oviduct. It is important to note that no direct connection exists between an ovary and its oviduct as is the case in the testis and vasa efferentia. Furthermore, there is no connection between the oviducts and the ureters from the kidneys. The oviducts are a separate pair of tubes, and they function solely in the transfer of the eggs. Each oviduct is a comparatively large, convoluted tube connected directly with the cloaca and ending anteriorly in close proximity, but slightly anterior, to the ovary of the corresponding side. The ovarian end of each oviduct is enlarged, funnel-shaped, and lined with ciliated cells. The current set up in the body fluids by the ciliary action draws the eggs into the oviducts and starts them on their journey from the body. The cloacal ends of the oviducts are enlarged to provide an egg-storage space near the opening into the cloaca in which the eggs remain for some time before being discharged through the cloaca. The eggs, when released from the ovary, are enclosed in a thin transparent covering, the vitelline membrane. As they pass through the oviduct, additional covering layers of a gelatinous material are secreted by glandular cells present in the lining of the oviducts. These gelatinous layers remain intact until a well-developed, active embryo is formed which is able to force its way through them.

Pairing of the male and female frogs occurs when the gametes are mature. During amplexus there is synchronous discharge of the sperm and eggs into the water, and this greatly enhances the possibility of

fertilization. In their movements through the water, there is the possibility that the sperm are attracted to the eggs by chemical substances released by the eggs. Such sperm-attracting substances have been demonstrated in certain organisms.

Development of the Frog's Egg.—The telolecithal frog's egg is visible to the naked eye as a tiny sphere, about the size of a pellet of tapioca. It is more or less clearly divided into a dark-colored animal pole and a light-colored, yolk-containing vegetal pole. Following fertilization, in which the union of male and female nuclei to form the synkaryon occurs, the fertilized egg, or zygote, begins to divide mitotically into daughter cells which remain in close contact, enclosed within the original vitelline membrane. Should it happen that some of the eggs are not fertilized owing to a failure of the sperm to reach them, they will, of course, not develop and soon begin to disintegrate. The first cell division, or cleavage, of the zygote, which begins shortly after fertilization, is first visible externally in the animal pole. The plane of cleavage is vertical; that is, it passes through both the animal and vegetal poles, dividing the embryo into two equal-sized daughter cells. The second plane of cleavage is also vertical and divides each of the first two cells in half, thus forming four equal-sized cells. The third plane of cleavage is horizontal, at right angles to the first two, is entirely in the animal pole region, and results in the formation of the eight-cell stage; consisting of four small cells from the animal pole, and the same number of larger cells from the vegetal pole. Thus, beginning at the third cleavage, an apparent retardation of cell division occurs in the vegetal pole due to the greater concentration of inert yolk material in this region. This becomes increasingly evident in the succeeding divisions. (Fig. 155*A* to *D*.)

Beginning at about the 24-cell stage, formation of the one-layered blastula is indicated internally by the development of a central cavity, or blastocoel, situated largely in the animal pole. The microscopic study of sections through an embryo in the early blastula stage shows that the blastocoel is enclosed above by a single layer of the pigmented cells of animal pole and, below, is bounded by the larger cells of the vegetal pole. Thus the blastula stage of the embryo may be described as a one-layered organism built around a central cavity, or blastocoel. This first cellular layer of the embryo is known as *ectoderm* and constitutes one of the three primary germ layers from which all of the tissues and organs of the adult organism gradually arise. The other two primary germ layers, endoderm and mesoderm, develop somewhat later, as will be shown in the following paragraphs. (Fig. 155*D* to *F*.)

Following the one-layered blastula stage, the next great landmark in embryonic development is the two-layered gastrula stage which is formed by a turning in, or invagination, of rapidly dividing ectoderm cells to form a new inner layer of cells, the endoderm, the second of the primary germ layers. In homolecithal eggs, the process of gastrulation may be crudely compared with pushing in the wall of a lightly inflated, thin-walled rubber ball with the thumb. If the wall is thus pushed in until it reaches the opposite pole of the ball, it is easy to see (1) that a two-layered condition results; (2) that the original cavity of the ball, corresponding to the blastocoel of the blastula, is obliterated; and (3) that a new cavity surrounding the thumb is formed. This latter cavity in the gastrula is lined with the invaginated endoderm and will shortly function as a primitive nutritive cavity or enteron. (Fig. 155*G*, *H*.)

In the telolecithal egg, as in the frog, the process of gastrulation is considerably modified and retarded by the inert mass of yolk in the vegetal pole. Basically, of course, gastrulation is the same in all types of egg in that it results in the formation of a two-layered embryo. In the frog embryo, this condition is reached in part by the overgrowth and in part by the synchronous invagination of the ectoderm cells from the animal pole. As a result of the overgrowth, the cells of the vegetal pole are gradually and increasingly covered by the pigmented ectoderm cells moving down from the animal pole. Synchronously, an underlying endoderm layer is being formed within. Invagination begins in a definite region of the egg, known as the *gray crescent*, which lies in a restricted area of the animal pole. This invaginating area soon becomes circular in outline and is gradually reduced in diameter as the ectoderm cells cover over more and more of the vegetal pole. Finally, at the conclusion of gastrulation only a tiny area, the yolk plug, of the light-colored yolk cells remains visible externally, surrounded by the circular opening in the ectoderm. This opening through which the yolk plug is seen is known as the *blastopore*. It indicates the posterior end of the embryo and the approximate position of the future anal opening. (Fig. 155*H*.)

If the embryo were transparent, it would be possible to observe under the microscope that other important internal changes, in addition to the formation of the endoderm, were under way. Thus, before gastrulation has proceeded very far, the third primary germ layer, or mesoderm, begins to develop dorsally between the previously formed ectoderm and endoderm. And so the two-layered gastrula gradually changes into the final three-layered condition. In a transparent embryo, it would also be possible to see the gradual develop-

ment of the endoderm, as it increases from a few cells to a distinct layer with many cells. And, just as was noted above in the development of the homolecithal egg, the continued development of the endoderm results in the obliteration of the original blastocoel and the formation of a new endodermal-lined cavity, the enteron, which is the forerunner of the alimentary canal. The latter gradually evolves into a tubular structure, but not until considerably later does it open to

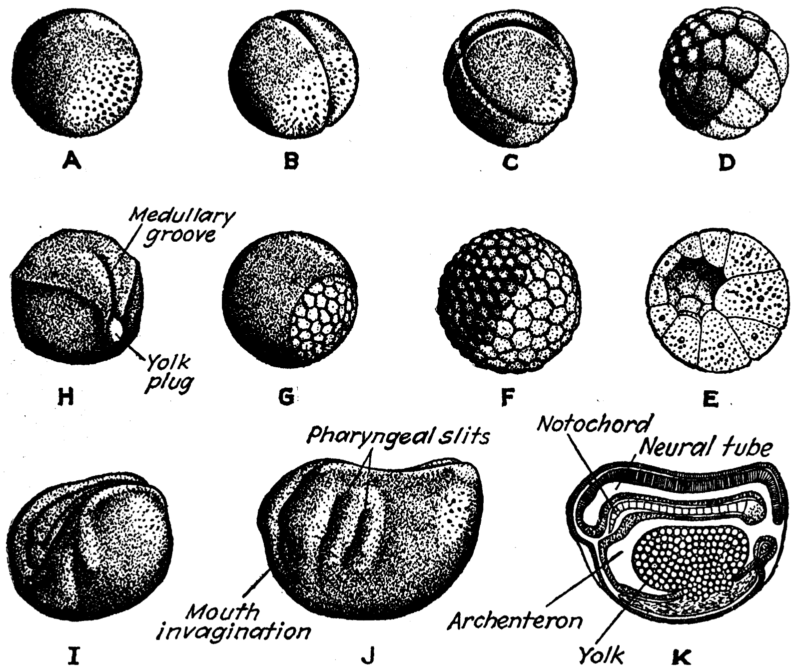


FIG. 155.—Early stages in the development of the frog. *A*, one cell; *B*, two cells; *C*, four cells; *D*, blastula, many cells; *E*, section of *D* showing blastocoel, *F*, late blastula; *G*; gastrula, early; *H*, medullary plate; *I*, formation of neural tube and elongation of body; *J*, tail bud stage; *K*, median section through *J*. (*Wolcott, from various sources.*)

the exterior through mouth and anus. Another important landmark in vertebrate development is the formation of an anteroposterior rod-like axis, the notochord, which differentiates from the mesoderm along the median dorsal line, between the ectoderm and endoderm. The notochord is the original foundation for the segemented bony vertebral column that later develops. (Fig. 155*K*.)

An external examination of the embryo near the close of gastrulation reveals a definite flattening of the future dorsal surface to form the medullary plate. This constitutes the first visible evidence of the establishment of a central nervous system. Observations on the

living embryo show that the edges of the medullary plate gradually become thickened and elevated above the surface of the embryo to form the medullary folds. A little later, these two medullary folds, extending the length of the body, meet in the dorsal mid-line and fuse, thus forming an ectodermal neural tube. From the latter, the brain, spinal cord, and other elements of the highly differentiated nervous system gradually arise. (Fig. 155*H*, *I*.)

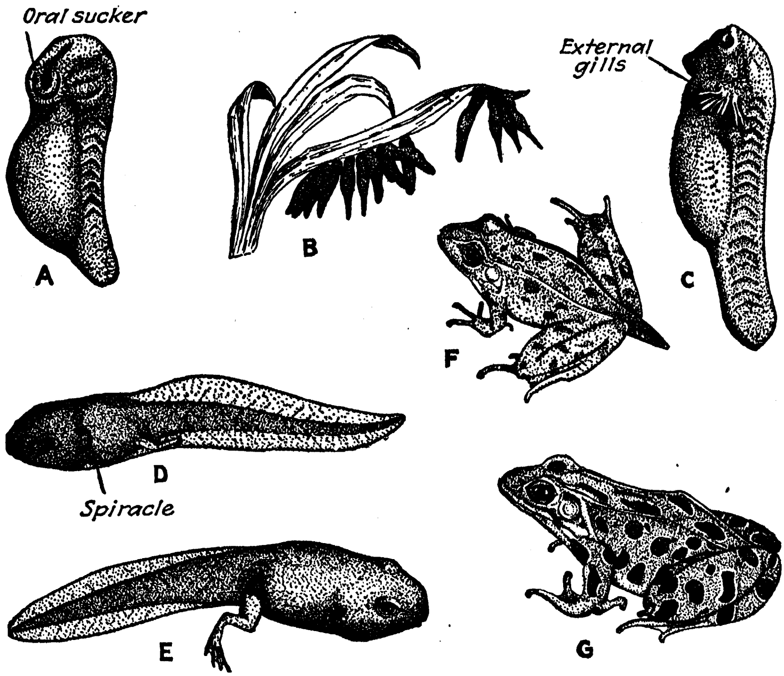


FIG. 156.—Late stages in the development of the frog. *A*, embryo with oral sucker for attachment to water plants as in *B*; *C*, external gills; *D*, much later stage at the beginning of metamorphosis, with internal gills and hind legs; *E*, embryo with large hind legs and shrinking tail; *F*, young frog with four legs and stump of tail; *G*, adult grass frog (*Rana pipiens*). (*Wolcott, from various sources.*)

And now the embryo definitely begins to lose the spherical shape of the original egg stage and to stretch out in an anteroposterior direction, and, shortly, definite body regions can be identified. Anteriorly, the general shape of the head is indicated, while posterior to it on each side of the body, the ectoderm is noticably thickened and elevated to form prominent gill arches through which, later, the paired lateral openings, or gill slits, break through the body wall into the anterior pharyngeal region of the alimentary canal. Certain surface swellings in the head region give evidence of sense organ formation.

A depression on the ventral surface of the head region indicates the position of the future mouth opening, and a similar depression at the posterior end of the body, just above the original blastopore, marks the rudiment of the anus. Posterior to the mouth area, a crescent-shaped region indicates the developing ventral sucker which is of use in the later tadpole stage. A rounded, knob-like dorsal projection at the extreme posterior end of the body is known as the tail bud. It gradually extends posteriorly and develops into the long, muscular tail. During all the changes so far, the embryo has not taken in any food from the environment; nourishment has been secured by the continued utilization of food materials stored in the vegetal pole of the egg during ovarian development. Even at the tail bud stage, the ventral and posterior regions of the embryonic body still contain a considerable quantity of available yolk. (Figs. 155*J*; 156*A*.)

Rapid growth continues, and in a few days after fertilization, depending to a considerable extent upon the temperature conditions in the environmental waters, the embryos attain the free-swimming tadpole stage in which head, trunk, and tail are definite structural entities. The active tadpoles soon hatch; that is, they emerge from the surrounding gelatinous capsules originally secreted in the oviducts. For a short time, external respiratory organs, the filamentous, branched gills, are present. These develop as outgrowths, or projections, from the gill arches on each side of the body, just posterior to the head. The external gills persist only temporarily and are soon replaced by internal gills lying in the gill slits. Water currents continually pass through the gill slits en route from the pharynx to the exterior. (Fig. 156*C*.)

In the young tadpoles, rudiments of the eyes, nose, and ears can be clearly identified in the head region. Dorsally, along each side of the body, the outlines of the primitive muscle segments, or myotomes, can be seen through the thin outer covering of ectoderm. The myotomes develop from the mesoderm layer which forms in two sheets, one lying on either side, that is, to the right and left of the neural tube and notochord. The mesodermal sheet on each side of the body grows ventrally and soon becomes differentiated into a dorsal portion, the vertebral plate, and a ventral portion, the lateral plate. The vertebral plates soon show evidences of segmentation and become divided into the segmented myotomes which later become associated with the vertebral column. The lateral plates do not become segmented but extend ventrally on each side of the body until they finally meet in the mid-ventral line, thus forming a complete layer of mesoderm lying just under the ectoderm. As the mesodermal tissue

of the lateral plates is extending ventrally, it is also dividing into an outer somatic layer and an inner splanchnic layer. The somatic layer of mesoderm is responsible, primarily, for the musculature of the body wall, while the splanchnic layer encloses the endoderm of the primitive gut and gives rise to the supporting, vascular, and muscular elements

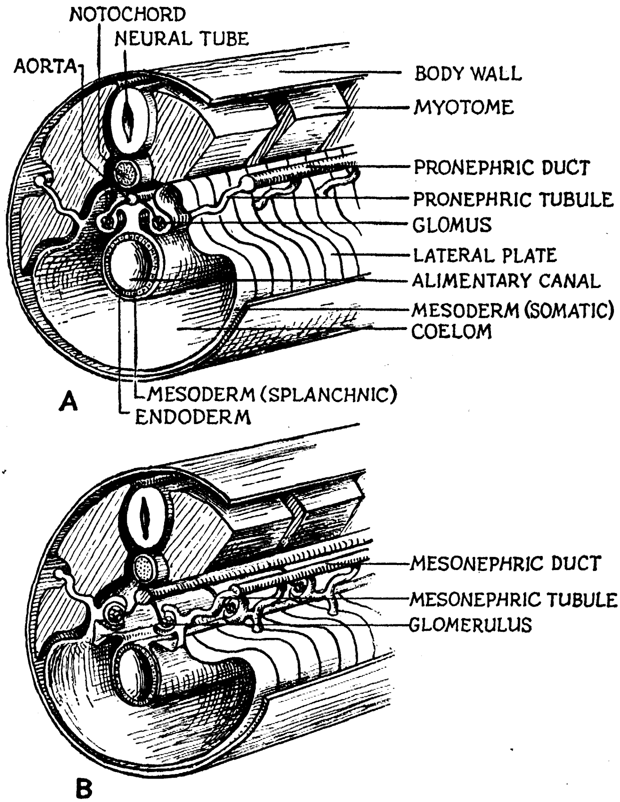


Fig. 157.—Diagrams illustrating the general body plan (*A*) of a primitive vertebrate embryo with pronephros, in which the tubules open into the coelom; and a more highly developed vertebrate embryo (*B*), as in the frog, with mesonephros, in which the mesonephric tubules collect wastes from the blood stream through glomeruli as well as from the coelom. The differentiation of the mesoderm to form myotomes and lateral plates is clearly shown. (*Redrawn by L. Krause from Wilder, "History of the Human Body," Henry Holt & Company, Inc. Slightly modified.*)

of the alimentary canal. The space that develops through the splitting and separation of the somatic and splanchnic layers of mesoderm becomes the coelom. (Fig. 157.)

Tissue Differentiation.—Having traced the main features of development in the frog from the fertilized egg to the well-developed, free-swimming tadpole, it will be desirable at this point to summarize

the fate of the primary germ layers, ectoderm, endoderm, and mesoderm. Thus, embryological studies show that the superficial layers, or epidermis, of the skin as well as the basic tissues of the exoskeletal structures are of ectodermal origin. The crowning achievement of the ectoderm, however, unquestionably lies in the formation of the all-important nervous system and associated sensory elements which permeate every possible niche and thus establish control throughout the entire organism. As is evident from the material presented in the previous chapter, the nervous system is not only the most highly differentiated of all the organ systems but the one assigned to administer all of the essential functions of the living organism.

The endoderm is the great nutritive layer of the body. The primitive gut, or enteron, which begins its development during gastrulation is entirely endodermal, as has been noted above, and the functional cellular lining tissue in the permanent alimentary canal is directly derived from these original endoderm cells. A portion of the mouth cavity (stomodaeum) and a small area at the extreme posterior end of the alimentary canal (proctodaeum) is, however, lined by ectoderm. The endoderm, in addition to forming the functional lining of the alimentary canal, is also responsible for the formation of several important organs that are more or less closely associated with the nutritive system, including the liver, pancreas, thyroid glands, lungs, and bladder. All of these organs develop in much the same way by an outgrowth of the endodermal wall of the enteron at an early stage to form either single or paired rudiments. In this connection, a basic fact should be recognized, namely, that the vertebrate organs, in general, are not wholly formed from a single tissue but represent a structural and functional mosaic of various tissues. Thus the hepatic cells of the liver are endodermal in origin, but the complete organ also contains vascular and connective tissues derived from the mesoderm together with nerve elements that are ectodermal in origin.

From the important mesoderm layer comes three great organ systems: the vascular, muscular, and skeletal, all of which are widely distributed throughout the entire body. Previous mention has been made of the division of the mesoderm into the vertebral and lateral plates (page 298). The vertebral plate myotomes, with the somatic layers formed from the lateral plates, are responsible for the muscle tissues present in the body wall and in the appendages, as well as for the connective tissues and vascular elements. These same tissues surrounding the endodermal lining of the alimentary canal develop from the splanchnic mesoderm (Fig. 157*A*). Both the somatic and splanchnic mesoderm layers contribute to the formation of the peri-

toneum, which forms a continuous lining layer throughout the coelom as well as a covering tissue for the various organs. From the peritoneum arise the mesenteries by means of which the various organs are suspended from the walls of the coelom. Finally, the functional elements of the urogenital system are mesodermal in origin. (Fig. 157.)

The study of the life cycle of the frog, and of the great majority of amphibia, shows that the aquatic fish-like tadpole stage is only temporary. Metamorphosis occurs after some weeks, and the tadpole changes into the air-breathing, four-legged adult frog. Experimental work has definitely shown that the metamorphic processes in the amphibia are incited and regulated to a great extent by the thyroid hormone. The chief structural changes in metamorphosis are concerned with the development of the forelegs and hindlegs, the degeneration of the tail, and changes in the alimentary canal and the respiratory mechanism. The nutritive system of the tadpole, with a very long, coiled intestine, is equipped for an herbivorous diet. The metamorphic changes remodel this system and adapt it for the more concentrated carnivorous diet of the adult. Metamorphic changes are also of a radical nature with respect to respiration. The gill tissues degenerate, and so the animal is no longer able to secure oxygen from the water. Air must be forced into the lungs which, though present for some time, have not hitherto functioned. (Fig 156*D* to *F*.)

DEVELOPMENT OF THE CHICK

With the main features of amphibian development in mind, we may now pass to a consideration of avian embryology which, though conforming to the main features exhibited in the frog, presents certain distinctive features of particular importance for acquiring a satisfactory understanding of human development, our final goal. The characteristic developmental processes of the birds are basically grounded in the provisions for the internal fertilization and for nourishing the embryo and represent a climax in the storage of food in the telolecithal egg as has been indicated above.

Reproductive System.—We may begin our discussion with the reproductive system of the hen, which, it may be stated, is an unpaired structure in the adult developed originally on the left side of the body. The corresponding organs of the right side are present in the embryo but undergo degeneration in the female before maturity is reached. This condition does not obtain in the male; both of the testes and the associated ducts persist and function in the adult. The ovary, examined with the naked eye, is seen to consist for the most part of a mass of projecting yellowish globules of various sizes

in which the eggs are undergoing development. Lying near the ovary is a large convoluted oviduct which ends anteriorly in a ciliated opening, the ostium. Posteriorly, the oviduct connects with the

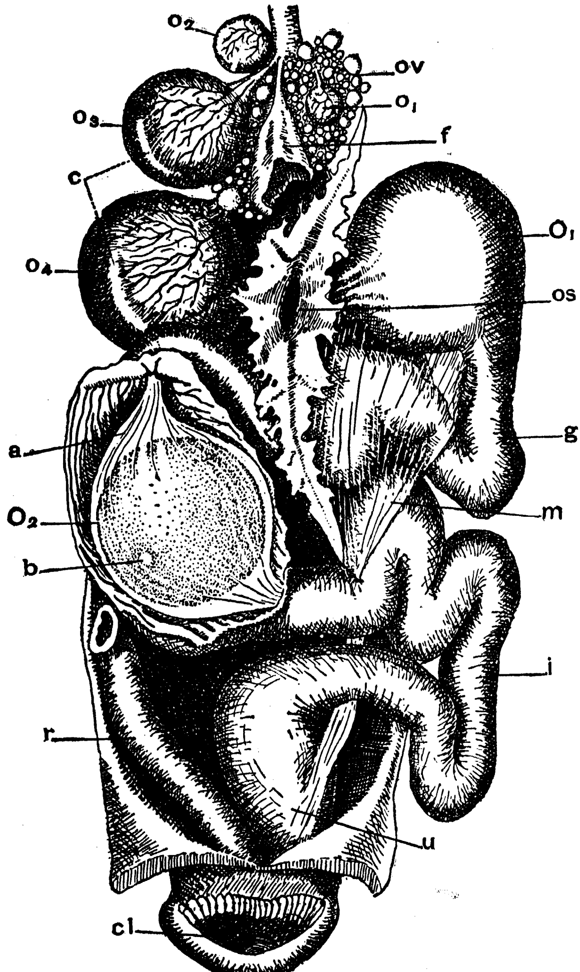


FIG. 158.—Reproductive system of the hen. The single ovary is shown above, with numerous ovarian eggs in various stages of development (o_1, o_2, o_3, o_4). The oviduct with opening, or ostium (*os*), is shown with two eggs (O_1, O_2), though normally only one egg passes through the oviduct at a time. The oviduct has been opened at one place to show the egg (O_2) with blastoderm (*b*) and the albumin (*a*) which is being secreted. *c*, cicatrix; *cl*, cloaca; *m*, mesentery; *r*, rectum; *u*, uterus. (*Wieman, after Coste-Duval.*)

cloaca. The oviduct consists, first, of the ostium, just noted. It is followed by a glandular portion lined with secreting cells that form the so-called white, or albumin, enclosing the yolk and also further

posteriorly, the outer membranes and the calcareous shell as well. All of the materials are formed as secretions from the glandular lining cells. A short, thin-walled, distal region of the oviduct posterior to the secreting areas leads directly into the cloaca. (Fig. 158.)

The egg cell or yolk, as it is commonly termed, when released from the ovary is drawn at once into the near-by ostium to begin its passage down the oviduct. The yolk material is enclosed in a transparent vitelline membrane. Provided mating with the male has previously occurred, the sperm deposited in the cloaca of the female will have found their way up the oviduct. Accordingly, it is possible for the egg to be fertilized shortly after it enters the oviduct. Cleavage in the zygote then begins. As noted earlier, the large amount of food material present in the hen's egg makes total division impossible so that only partial, or meroblastic, cleavage takes place. Cell division is confined to the tiny disc-like blastoderm lying on the upper surface of the yolk. As cell division continues and additional food material is utilized, the blastoderm increases in size and gradually spreads over and encloses the inert mass of yolk. Thus at the end of about 5 or 6 days' incubation it will be found that the actively growing tissues of the blastoderm completely cover the yolk area. (Fig. 158.)

Development of the Hen's Egg.—In the hen, ovulation occurs independently of pairing, but, of course, such unfertilized eggs are infertile. As the egg passes down the oviduct, the lining cells secrete several layers of albumin. A portion of the albumin lying next to the vitelline membrane is drawn out to form a pair of spiral-shaped chalazae, situated at opposite poles of the yolk. The chalazae prevent the yolk-mass from turning end for end in the egg but at the same time permit it to revolve with the shell when the latter is turned over and over on its short axis. Thus, when the egg comes to rest, the blastoderm is always found lying above the yolk and can be seen when an opening is made through the shell. In the great majority of hen's eggs there is a definite orientation of the anteroposterior axis of the embryo so that, when the observer places the large end of the egg to his left, the axis of the embryo will be at right angles to the long axis of the egg, with the head end pointed away from the observer. (Fig. 159.)

After the layers of albumin are secreted around the yolk, other glandular cells lying distally secrete a double shell membrane which forms a flexible resistant covering around the albumin. At the large end of the egg, these two membranes are separated so that an air space lies between them. Finally, the hard calcareous eggshell is also formed as a secretion, after which the egg is ready to pass into the cloaca and out of the body through the cloacal opening. The passage down the

oviduct normally requires 24 hours, so that, if the egg is fertilized in the anterior end of the oviduct, the blastoderm will have reached the 24-hour stage of development at the time the egg is laid. Further development of the blastoderm cells then ceases until the proper temperature is supplied. This is approximately 103°F., corresponding to that of the parental body tissues. The few cells, which constitute the partially developed embryo in the blastoderm of the egg at this stage of development, will remain dormant for several days without injury and then begin active developmental processes again when incubated in the normal manner by a hen or artificially in an incubator if the proper temperature is supplied. (Fig. 159.)

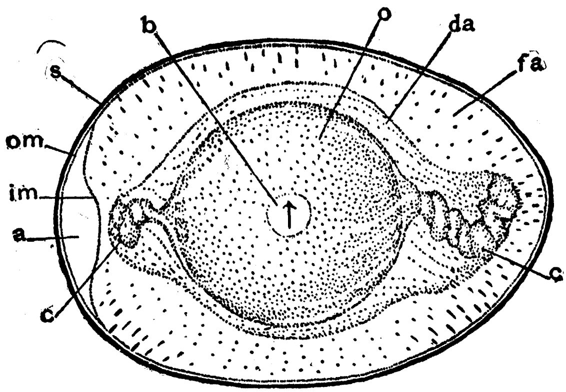


FIG. 159.—Diagram illustrating the internal structure of the hen's egg. *a*, air chamber; *b*, blastoderm. Arrow points towards the head end of the embryo. *c*, chalaza; *da*, *fa*, albumin; *im*, inner shell membrane; *o*, the yolk, the egg proper, formed in the ovary; *om*, outer shell membrane; *s*, shell. (*Wieman.*)

The continued division of the blastoderm following fertilization finally results in the formation of a great number of irregularly shaped cells with the smallest ones near the center of the blastoderm. Shortly, these primitive ectoderm cells arrange themselves in a bridge-like structure which overlies a small cavity, the blastocoel, near the upper surface of the yolk mass and just underneath the original blastoderm. This chick blastocoel is comparable to that found in the blastula stage of the frog embryo as previously described. The assemblage of ectoderm cells above the blastocoel in the chick embryo constitute the blastula proper. Thus the blastula of the chick consists of a flattened or disc-like layer of cells lying above the blastocoel and also above the large yolk mass, rather than a spherical body of cells enclosing the blastocoel as noted in the frog. (Fig. 155*E*.)

Continuing our description of early chick development, it will next be found that the ectoderm cells, in the region of the blastoderm

destined to become the posterior end of the animal, begin to divide more rapidly than in other areas. As a result, a sheet of cells is turned under the ectoderm and starts to invade the cavity of the blastocoel as a second, or endoderm, layer; synchronously forming a new cavity, the enteron or primitive gut. This is, of course, the process of gastrulation. The new endoderm layer spreads anteriorly and laterally under the outer ectoderm, and soon both of these layers extend to the periphery of the blastoderm. At about the 18-hour stage of incubation, a thicker region, the primitive streak, is clearly marked in the center of the blastoderm, and this indicates the establishment of the embryonic anteroposterior axis. The primitive streak is primarily due to a concentration of ectoderm cells along the median line of the blastoderm. It is in this region that the mesoderm layer begins to develop. The first mesoderm cells migrate laterally from the posterior part of the primitive streak, but, as more and more are formed, they spread anteriorly as well as laterally thus in time forming a complete layer of mesoderm between the ectoderm and the endoderm (Fig. 160*A*).

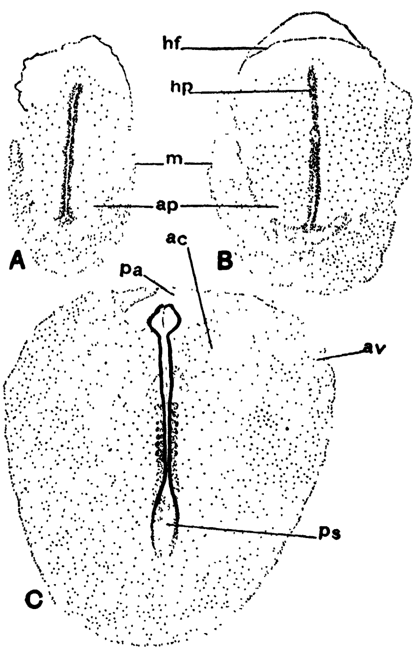


Fig. 160.—Early stages in the development of the chick embryo. *A*, primitive streak stage (18 hours); *B*, head process stage (20 hours); *C*, embryo with seven pairs of somites (24 hours). *ac*, amniocardiac vesicle; *ap*, area pellucida; *av*, area vasculosa; *hf*, head fold; *hp*, head process; *m*, margin of mesoderm; *pa*, proamnion; *ps*, primitive streak. (*After Wieman.*)

Just anteriorly to the primitive streak region, a concentration of ectoderm cells forms an anterior thickening, known as the *head process*, which soon involves all three germ layers. The region of the blastoderm in which the head process develops contains the rudiments of various embryonic body structures. The next notable development in this region is seen in the arrangement of the ectoderm cells to form the medullary plate and, from the latter, the formation of a definite neural tube by the elevation of the lateral edges and their fusion in the median line as previously described in the frog. Coincident with these activities, notochord formation and the differentiation

of the mesoderm to form the segmental myotomes are started. The latter, as in the frog, soon show a division into dorsal and lateral portions and also the formation of somatic and splanchnic mesoderm with the coelom between. All of these developmental features are well under way during the first 24 hours of incubation (Fig. 160*B*.)

From the description just given of the blastula and gastrula stages, it is evident that the really distinctive feature of early chick development is the fact that the embryo in the blastoderm area is spread out flat on the surface of the yolk. As a result, the rudiments of the various embryonic structures are formed in right and left halves lying on either side of the median anteroposterior axis of the body. These lateral, organ-developing areas constitute the extra-embryonic regions. At the 20- to 24-hour stage of incubation the embryo begins a process of folding which gradually separates it from the yolk mass and brings the right and left half of each organ in contact along the mid-ventral line where they unite to form the complete structure. The first of these folds (head fold) appears just anterior to the head region. A little later, right and left lateral folds are indicated which move in from the sides, and, finally, a tail fold is formed which progresses anteriorly. The final results are shown in the formation of the various organs by the union of the two halves and in the almost complete separation of the body of the embryo from the yolk material. Thus, after about 96 hours' incubation, it is found that the well-formed embryo is attached to the yolk sac by only a short tubular yolk stalk. The latter is filled with blood vessels through which the circulating blood, laden with absorbed food materials from the extra-embryonic areas, passes into the body of the embryo. (Fig. 167*A*.)

Two-day Chick Embryo.—By the end of the second day of incubation, the embryo has attained a greatly increased size as compared with that of the tiny blastoderm. The anterior end of the embryonic body is folded from the yolk sac and is lying on its left side, whereas the posterior part of the body is still flat on the yolk. As a result, the embryo is shaped somewhat like a reversed question mark, with the anterior end of the body bent (cervical flexure) toward the right at an angle of almost 90 deg. The rudiments of the various organ systems are now established; and some of them, notably the vascular system, are functioning. Particularly striking in the living two-day embryo is the beating heart, which at this stage is connected with blood vessels running through the tissues of the embryonic body and also out to the yolk regions. The growth of the extra-embryonic endoderm has put this nutritive layer in contact with the yolk so that the latter can be digested and absorbed. Also the extension of the extra-embryonic

mesoderm to the covering of the yolk sac makes possible the formation of a dense network of blood vessels for transporting the food materials absorbed from the yolk to the growing tissues of the embryo. The two-day heart has two chambers: an auricle and a ventricle. The auricle receives the extra-embryonic blood, rich with absorbed food material and laden with supplies of oxygen which have permeated through the shell and membranes of the egg. From the auricle the blood passes into the ventricle, and then it is quickly forced out through the connecting arteries to all the body tissues and back to the yolk sac for new supplies of food and oxygen. Gill slits, though non-functional in the chick, are present at this stage of development, and the blood leaving the ventricle is routed between them. They soon disappear as definite structures. (Fig. 161.)

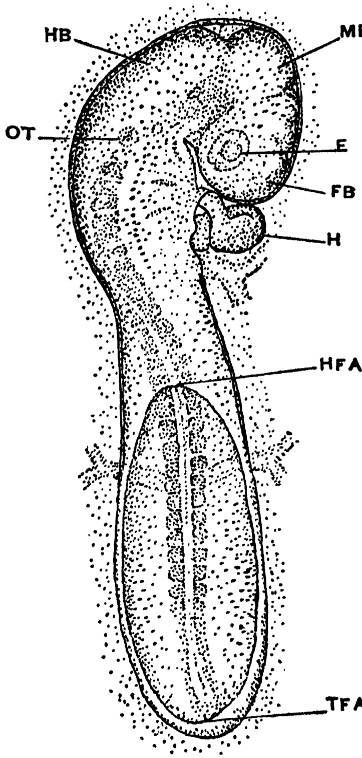


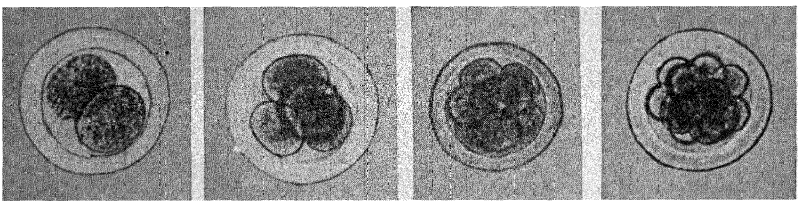
FIG. 161.—Chick embryo with 27 to 28 pairs of somites (48 to 50 hours). The head fold of the amnion (*HFA*) now covers the anterior two-thirds of the body. *E*, eye; *FB*, forebrain; *H*, heart; *HB*, hindbrain; *MB*, midbrain; *OT*, auditory vesicle; *TFA*, tail fold of amnion. (*Wieman.*)

The embryo is mostly enclosed by this time in a fluid-filled amniotic cavity. The amnion starts to develop in the ectoderm anterior to the head region and grows posteriorly over the embryo as an ectodermal sheet. Finally, with the aid of the lateral and posterior amniotic folds, a two-layered sac is formed over the entire embryo. And so, from the beginning of the second day of incubation to the fourth day, the embryo is being separated from the yolk sac by folds that grow *underneath* and at the same time enclosed by the amniotic tissues that lie *above*. The rudiment of another important embryonic membrane, the allantois, is first seen at about the 72-hour stage as an endodermal outgrowth from the primitive gut, just posterior to the yolk stalk. The allantois finally forms a large vascular-walled sac which lies close to the outer shell of the egg and functions, primarily, in the respiratory interchange. The yolk sac, the amnion, and the allantois constitute the important embryonic membranes of the chick. (Fig. 167.)

The development of the chick embryo continues, enclosed within the shell, for a normal 21-day incubation period. It utilizes the yolk material for nutrition and carries on the essential respiratory exchange through the permeable shell materials. When the proper stage of development has been reached, the chick breaks through the shell with the aid of a horny projection which develops as a dorsal outgrowth, near the tip of the beak. Leaving the shell behind, the chick walks out into the open as an active, independent individual able to secure food for continued growth.

MAMMALIAN DEVELOPMENT

It has previously been emphasized that the essential features of vertebrate development present a background of uniformity in the various types. The variable features appear to be basically associated



2 cells 4 cells 8 cells 16 cells

FIG. 162.—Photomicrographs of living eggs of rabbit: 2, 4, 8, 16 cells. (*Allen, after Lewis and Gregory.* "*Science in Progress,*" *Yale University Press.*)

with the embryonic nutrition which, in turn, is dependent upon the amount of food stored in the egg. A comparative study of mammalian development shows that the primitive group, the Prototheria, produce heavily yolked eggs, structurally very close to those of birds. Also, the prototherian eggs, after being internally fertilized, pass from the body of the female and undergo external development as do those of birds. Thus the Prototheria, which includes two well-known types, the duckbill (Ornithorhyncus) and the spiny anteater (Echidna), are oviparous. In all other mammals, however, both fertilization and embryonic development take place within the body of the female; that is, they are viviparous. And it is found that the typical mammalian egg is microscopic in size and with a minimum amount of stored food. The evidence is clear, however, from the study of the early developmental stages that a close structural relationship exists between the mammalian egg and those of reptiles and birds. (Fig. 162.)

The necessity of retaining the fertilized egg in the mother for intra-uterine development is evident from the fact that the mammalian eggs, as noted, contain a minimum of nutritive materials. Therefore, if

development is to continue beyond the early cleavage stages, an additional food supply must be established at once. This is accomplished in the mammals through the specialization of a portion of the oviducts to form the womb, or uterus, which permits the developing embryo to tap the essential nutritive supplies carried in the maternal blood stream. The extent of embryonic development occurring in the uterus varies considerably in the various mammalian groups. In the more primitive viviparous mammals, as exemplified in such Marsupials as the kangaroo and opossum, uterine development is terminated early, and the offspring are born in a comparatively immature condition. Accordingly, after they are born, it is necessary for them to find their place in a special external pouch, the marsupium. This pouch is located on the ventral abdominal wall of the female, with the mammary glands opening into it. The embryos are carried in the marsupium for some time and there nourished by the milk from the mammary glands until they reach a sufficient degree of maturity to take care of themselves. Even among the higher types of mammals, the maturity of the embryo at birth shows great variation. The uterine development of the offspring is highest in the hoofed mammals, or Ungulates, while in the Primates, the order to which Man belongs, a comparatively meager uterine development is found, and the child is born in an essentially helpless condition which necessitates parental care for a considerable period.

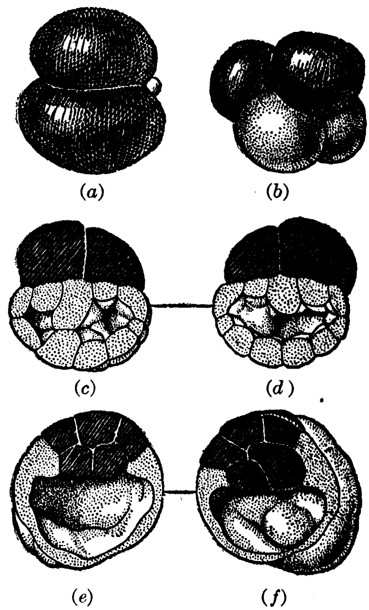


FIG. 163.—Drawings of wax-plate models illustrating the early cleavage stages of the mammalian egg (pig). *a*, 2 cells; *b*, 4 cells; *c* to *f* are sections showing differentiation of inner cell mass (dark cells) and the development of the segmentation cavity. The trophoblast arises from the cells shown in stipple. (*Stages selected from Wieman, after Heuser and Streeter.*)

If mating has occurred previous to ovulation, great numbers of sperm will be present in the oviduct, and fertilization will occur very quickly after the egg is released from the ovary. The cleavage of the yolkless mammalian egg is holoblastic and soon results in the formation of a tiny spherical body of cells, the morula, which externally appears essentially the same as the blastula of other holoblastic types. Internally, however, the cells of the mammalian morula show a much greater

differentiation than those of the blastula, with the rudiments of the three primary germ layers and the embryonic membranes definitely

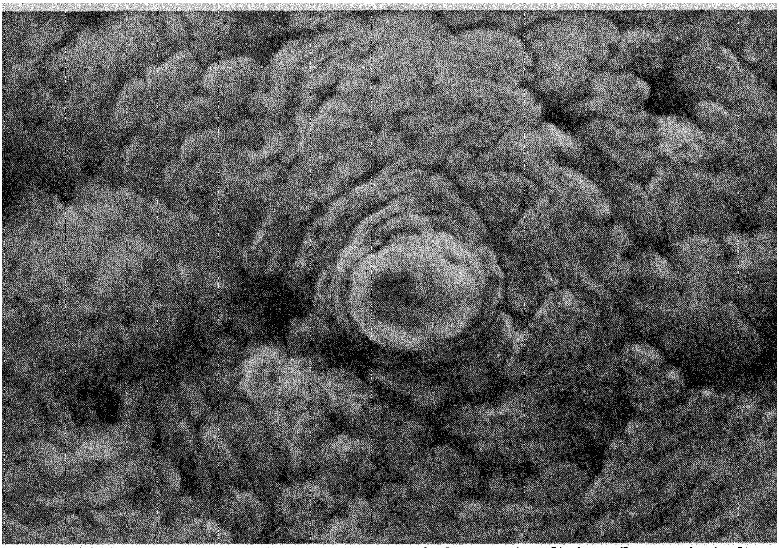


FIG. 164.—Photomicrograph of a portion of the uterine lining (human), indicating the implantation site of the embryo (elevated central area). *Cf.* Fig. 165. (*Scientific Monthly, January,* 1940. *Redrawn.*)

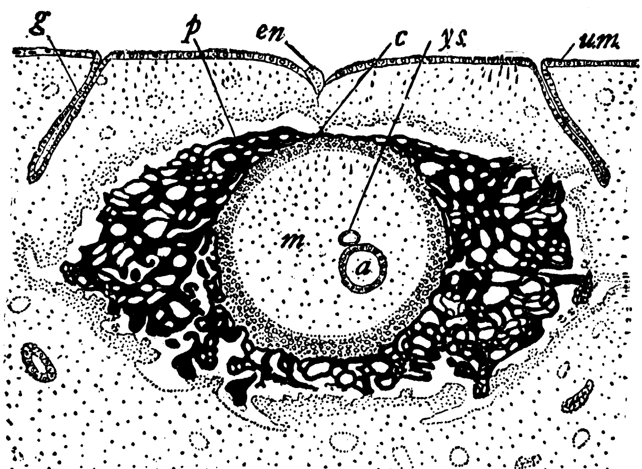


FIG. 165.—Vertical section through the wall of the uterus showing the implantation of a very early embryo (*Bryce-Teacher*). *a*, amniotic cavity; *c*, trophoblast; *en*, point of entrance of embryo closed by reunion of edges; *g*, gland; *m*, mesoderm (extra-embryonic); *um*, uterine mucosa (lining); *ys*, yolk sac. (*Wieman.*)

established. A section through the tiny spherical morula, prepared for microscopic study, reveals an outer covering of the primitive

nutritive ectoderm, or trophoblast, enclosing a central cavity. Suspended in the central cavity from the outer layer is a group of differentiated cells, the inner cell mass, which contains the tissue rudiments of the embryonic body. Examination of the inner cell mass shows that the rudimentary tissue layers are spread out flat over the yolk sac and covered above by the precociously formed amnion, essentially as in the chick embryo. Curiously enough, the tiny "yolkless" yolk sac under the embryo, though apparently homologous with that of the chick, is without nutritive function in the mammal. (Figs. 163, 165.)

The trophoblast, which, as just noted, forms the outer covering, is essentially a specialized nutritive tissue. It secretes enzymes which erode a tiny area in the lining of the uterus. This enables the embryo to embed itself in the maternal tissues and to secure nutritive materials from them. The passage of the zygote down the oviduct normally takes two or more days so that, by the time the uterus is reached, the trophoblast is ready to play its double role in aiding the attachment of the embryo and in securing food from the maternal tissues. For a time, nutritive materials are secured by the combined digestive and absorptive action of the trophoblast, but shortly, as the embryo continues to enlarge, a very remarkable organ of the pregnant mammalian female, the placenta, is formed by a combination of fetal and maternal tissues and is directly connected to the embryo by the umbilical cord. It is the placenta that permits the embryo to secure nutritive materials from, and give off fetal wastes to, the maternal blood stream. Early differentiation of the embryonic vascular system, extending through the umbilical cord, makes the rapid transportation of materials to and from the placenta possible. (Figs. 164 to 167.)

And so the placenta functions in the essential interchange of materials between the parasitic embryo in the uterus and the mother. Arteries of the maternal vascular system are continually bringing blood to the placenta with abundant supplies of food and oxygen. Maternal blood, carrying embryonic wastes which have been picked up during the passage through the placenta, leaves through the connecting veins. The arrangement of the human placental tissues is such that the maternal blood flows into large spaces, or sinuses, where it directly bathes the projecting finger-like villi. The latter are formed from embryonic tissues and contain a network of fetal blood vessels—both arteries and veins—extending through the umbilical cord and connecting with the vascular system of the embryo. The main vessels, through which blood passes from the embryo to the placenta, are the umbilical arteries. Such blood is loaded with the nitrogenous wastes and carbon dioxide excreted by the embryonic

tissues. During its circulation through the capillary networks in the placental villi, these wastes are released. They pass through the walls of the villi, are picked up by the maternal blood stream and then are excreted from the body of the mother through the lungs and kidneys. Synchronously, the supplies of food and oxygen present in the arterial maternal blood are released in the placental tissues and pass through the walls of the villi and into the fetal blood. The latter,

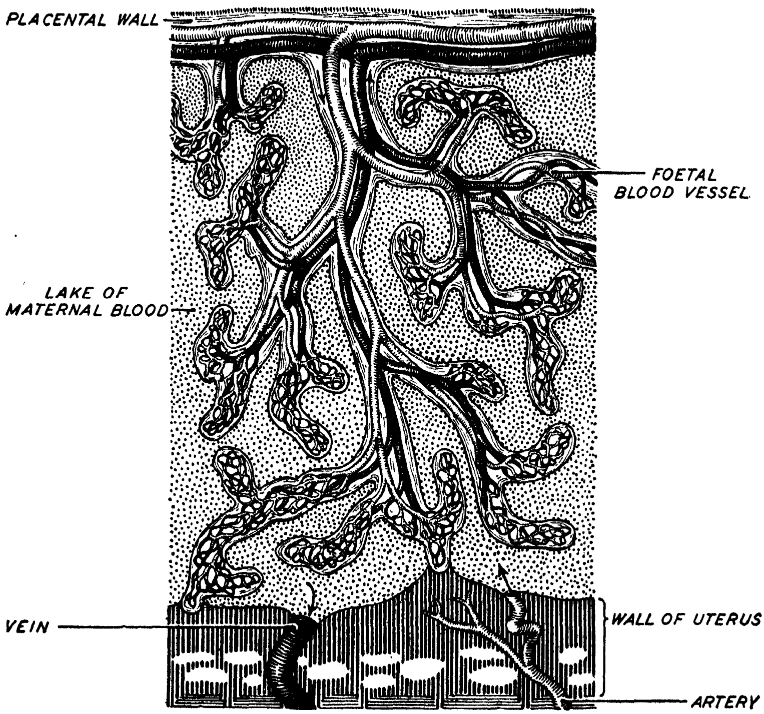


FIG. 166.—Vertical section through the human placenta attached to the wall of the uterus (below). This shows the fetal blood vessels surrounded by "lakes" of maternal blood. Note that there is no direct connection between the circulatory system of the mother and child. (*Buchanan, "Elements of Biology," Harper & Brothers.*)

now freed from the excess wastes and laden with the substances necessary for the embryonic tissues, passes by way of the umbilical veins back to the embryo for circulation through the body. It should be emphasized that the vessels of the vascular systems of mother and child are not directly connected in the placenta or elsewhere. All interchange of materials between fetal and maternal blood must, therefore, take place by diffusion through the placental tissues. The duration of uterine development, or gestation, varies considerably in the various mammalian groups. For example, the mouse embryo

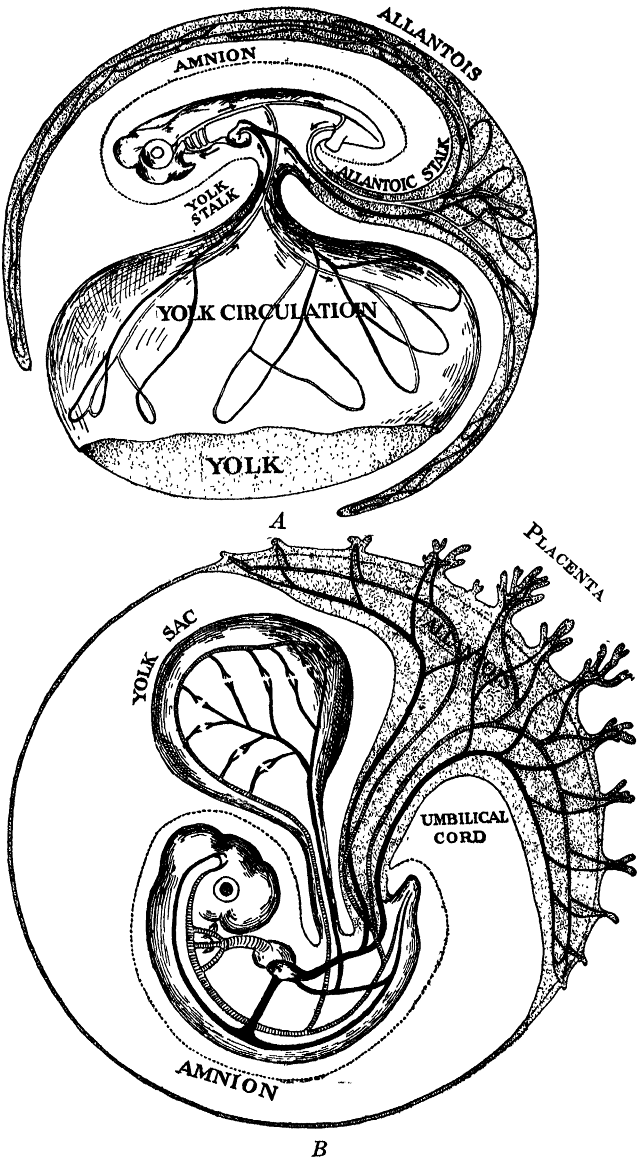


FIG. 167.—Diagrams showing the relations between the embryo and the embryonic membranes (amnion, allantois, and yolk sac) in (*A*) the chick embryo and (*B*) a placental mammal, as man. (*Wilder, "History of Human Body," Henry Holt & Company Inc.*)

completes its development in the uterus in about 20 days, whereas the human gestation period is approximately 280 days. (Fig. 167.)

HUMAN REPRODUCTION

With the general plan of mammalian reproduction in mind, consideration may be given to the main features of human reproduction, with particular reference to the structural and functional features of the male and female reproductive systems.

Male Reproductive System.—The reproductive system of the human male follows the general vertebrate pattern in its basic structural features but is more highly developed and more closely associated with the vascular, endocrine, and nervous systems. The essential sperm-producing testes are two in number. They develop originally within the body cavity, lying close to the kidneys. Before birth, however, the testes migrate posteriorly, pass through the inguinal rings located in the abdominal wall on each side of the body, and, finally, take their position outside the body cavity in a soft-walled sac, the scrotum, which is primarily attached to the bony pubic arch. Each testis is seen as an oval-shaped body which hangs suspended in the scrotal sac by the attached spermatic cord. The latter is a composite structure containing the arteries, veins, and nerve fibers supplying the testicular tissues and also a portion of the sperm-conducting tubule, or vas deferens. All the elements of the spermatic cord are permeated and enclosed by connective tissues which, in turn, are continuous with the tissues of the body wall surrounding the inguinal ring. (Plate XVI*A*.)

The scrotum is a more complex organ than is generally realized. It is essentially a two-layered sac with the constituent tissues merging with those of the body wall to which it is attached. The outer covering of the scrotum consists of a layer of skin, more or less folded and enclosing a second layer consisting largely of smooth muscle tissue. From the latter, a median fold arises which, projecting anteriorly, divides the scrotum into the right and left chambers, each of which is occupied by the corresponding testis. Functionally, it appears that the scrotum acts as a temperature regulator for the delicate male germinal cells undergoing development in the gonads. Thus when the external temperature is lowered, as in a cold bath, the scrotal tissues contract, and the testes are drawn anteriorly, close to the body wall. The opposite condition is found when the external temperature is too high, for the scrotal tissues then relax, thereby greatly increasing the size of the scrotum. The testes fall away from the body wall, and

enlarged surface areas of the scrotum are presented for cooling by surface evaporation.

Previously, a description was given of the microscopic structure of the vertebrate testis as seen in the frog, but it will be well to indicate certain additional features characteristic of the human testis though the general plan of structure is much the same throughout the vertebrates. The human testis consists of two portions: the sperm-producing portion, or testis proper; and the sperm-transporting portion, or epididymis. The body of the testis consists primarily of a great many

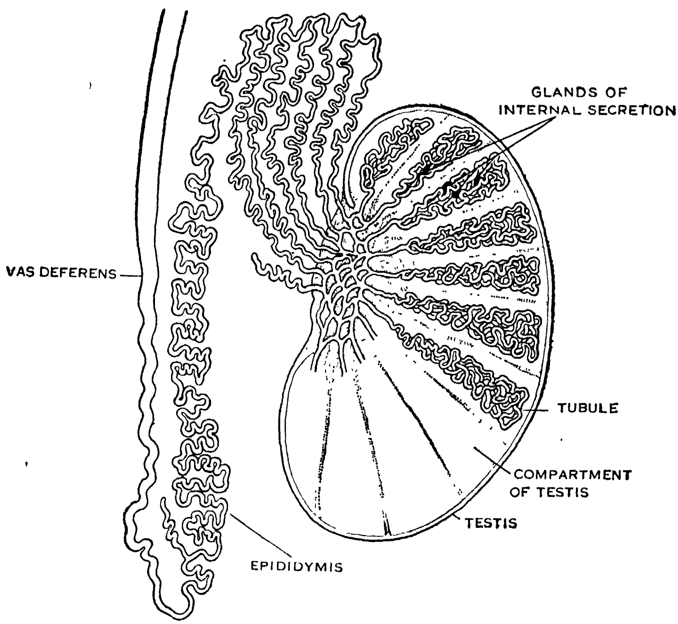


FIG. 168.—Diagram illustrating the general structural plan of the human testis and associated ducts. Diagrammatic. (*Haggard, "Science of Health and Disease," Harper & Brothers.*)

very fine convoluted seminiferous tubules, in the walls of which the sperm develop. (Fig. 168.)

Each of these male gametes exhibits a typical cellular structure in the early stages of development, but, after passing through the successive stages associated with sperm formation (spermatogonia, spermatocytes, and spermatids), it becomes a highly modified sperm cell, adapted for active movements in a liquid. A mature sperm, though minutely microscopic in size, is amazingly complex in its structural appointments. Three main divisions are noted, namely, (1) an anterior pointed portion, or head, which is really the essential

part of a sperm because it contains the chromatic material arranged in the gametic nucleus, which, as we know, is responsible for the transfer of paternal hereditary characters to the offspring; (2) a middle piece carrying the dynamic division center, or centrosome, to the fertilized egg; and (3) a vibratile tail, or flagellum, the movements of which are responsible for the locomotion of a sperm in a suitable liquid medium and for the ability to force its way through the resistant membranes of the egg. However, the movements of the mass of sperm from the testis and through the length of the urogenital canals, as well as their later discharge to the exterior, are primarily due to the action of the muscle tissue in the walls of the ducts rather than to individual locomotion.

The seminiferous tubules in the various areas are grouped in some 250 compartments, or lobules, formed by connective tissue partitions continuous with the outer connective tissue sheath (*albuginea testis*). Intermingled with the tubular sperm elements throughout the testicular areas are important endocrine elements in the interstitial tissue, which are responsible for the development of the secondary sex characters and the general control of the sex phenomena, as previously described in the chapter on Secretion (page 115). The seminiferous tubules converge toward the posterior testicular wall and there connect with the tubular network of the rete testis, which, in turn, is in direct connection with the long, greatly coiled tube of the epididymis. The latter is about 20 ft. in length and, distally, leads into the final and larger conducting element, the vas deferens, which passes through the spermatic tubule and enters the body cavity through the inguinal ring. The vas deferens from each testis joins the urethra carrying liquid wastes from the bladder. It is apparent that the urethra in the male serves as a common duct for both urine and semen in its extension from the vas deferens-urethral junction through the penis to the external opening.

Associated with the vas deferens are a number of other noteworthy structures which function in various ways, as will be indicated. Thus, a sperm reservoir, the seminal vesicle, opens into each vas deferens shortly before the latter joins the urethra. This junction forms the ejaculatory duct which, as the name indicates, forces the sperm stored in the seminal vesicles into the urethra. A glandular structure, the prostate gland, surrounds each ejaculatory duct close to the urethral opening, with a duct opening into the urethra below the opening of the vas deferens. The prostate glands give off a secretion of doubtful function which mixes with the sperm. Additional glandular material is received from another pair of tiny glands (Cowper's glands) situated close to each prostate and also opening into the urethra. Accordingly,

the complete seminal fluid is found to be a milky liquid made up of the various glandular secretions and normally containing some 70

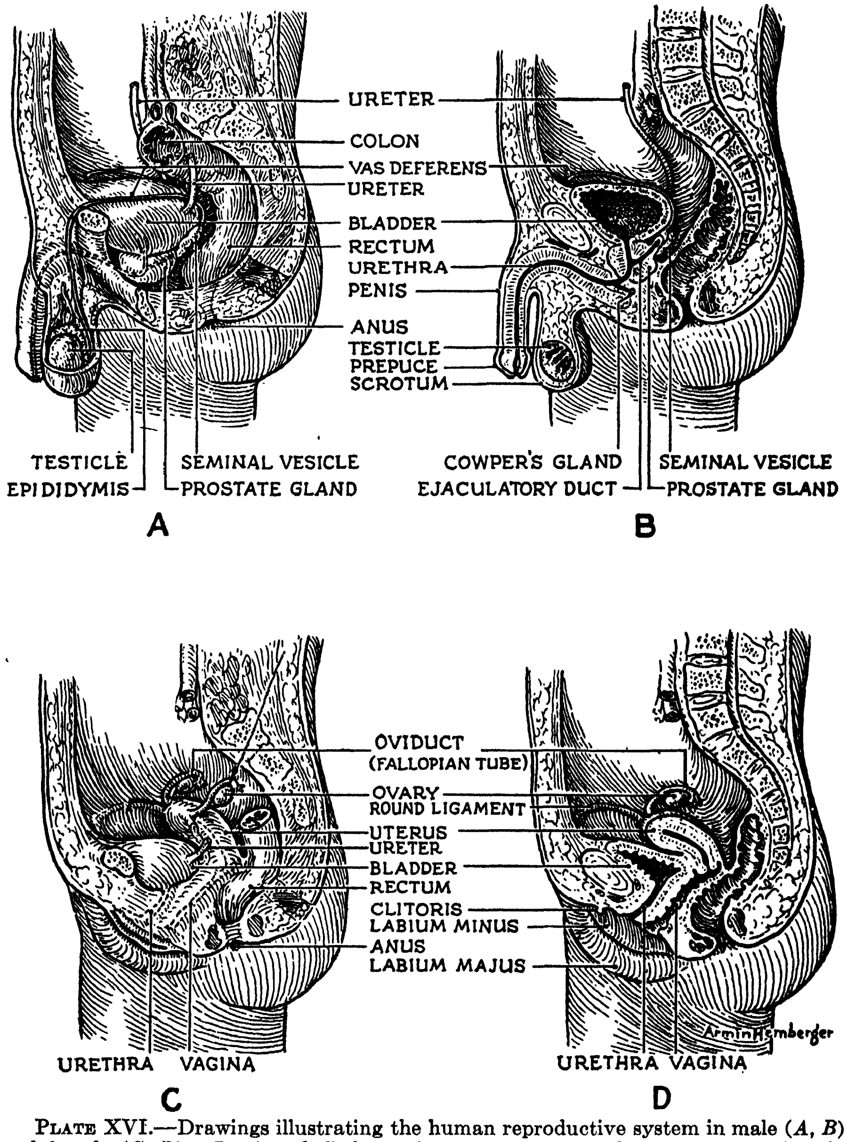


PLATE XVI.—Drawings illustrating the human reproductive system in male (*A*, *B*) and female (*C*, *D*). In *A* and *C* the various structures are shown in perspective; in *B* and *D* the structures are shown as seen in median sagittal sections.

million sperm in suspension in each cubic centimeter of fluid. Since from 3 to 5 cc. of seminal fluid are released at a normal emission, the

number of contained sperm is seen to be very large. The action of the ejaculatory ducts in forcing the sperm from the seminal vesicles into the urethra has been noted. Movement of the seminal fluid down the muscular-walled urethra is largely due to a reflex action of these contractile tissues, under control of the autonomic nerve fibers. (Plate XVI*A*,*B*.)

The penis, which serves as a common urinary and copulatory organ, reaches its full development only in the higher mammals. Thus in the prototherian mammals, in which a cloaca is present as in the birds, the penis is relatively undeveloped and remains concealed in the wall of the cloaca except when pairing takes place. In man, the penis is external and is attached primarily to the bony elements of the pubic bones, ventrally and in front of the scrotal sac; the skin of the body wall forming a continuous extension over it. Below the skin covering, the body of the penis is enclosed by a firm sheath composed largely of connective tissue elements and numerous unstriated muscle tissue fibers which radiate in all directions. Permeating these tissues are many large blood spaces, or sinuses, which, when filled with blood, increase the turgidity of the penis and thus cause its erection. The constituent connective and muscle tissues are arranged to form three main tubular bodies which extend throughout its length. These are designated as a pair of corpora cavernosa which lie toward the anterior surface, and the unpaired spongy body, or corpus spongiosum, lying below, that is, toward the posterior surface. The spongy body is penetrated throughout its length by the urethra and ends distally in a terminal enlargement, the glans penis, which it alone forms; the corpora cavernosa ending just back of the glans. The skin covering the penis is not attached to the tissues of the glans but projects over it as a loose circular fold known as the *foreskin*, or *prepuce*, which, normally, can be pushed back along the body of the penis, thus exposing the glans completely. Not infrequently the prepuce is drawn so tightly over the glans that it cannot be pushed back. In such cases, circumcision is indicated, a comparatively simple operation to which Hebrew male babies have long been subjected.

When functioning as a urinary organ, the penis is soft and flabby and in this position hangs pendant over the scrotum. As a copulatory organ, it is necessary that erection take place so that penetration can be made into the vagina of the female where the sperm are deposited. The act of erection is under the control of the parasympathetic nerve fibers originating in the lumbar region of the spinal cord and is accomplished by increasing the blood flow into the penis through nerve impulses passing over the vasodilator fibers to the muscle fibers in the

blood vessels and at the same time restricting the outflow of blood. As a result, the large sinuses present in the corpora cavernosa and the corpus spongiosum become filled with blood under considerable pressure. Also associated to some extent in the erective phenomena are the widely distributed muscle fibers.

Female Reproductive System.—Comparatively simple in the lower types of animals in which the gametes ripen only once a year and are then released for fertilization and development outside the body of the mother, the reproductive system of the vertebrate female exhibits increasing complexity as provision is made for ovulation at comparatively short intervals and for both fertilization and embryonic development to take place in the body of the mother, as in the human species. The essential egg-producing gonads in women consist of a pair of ovaries which develop and remain permanently located in the abdominal cavity, somewhat posterior to the kidneys. The ovaries are of comparatively small size, measuring only about 1½ in. in length, ¾ in. in width, and with a maximum weight of some 5 or 6 g., or about ⅕ oz. Histologically, the ovaries are found to consist very largely of a firm connective tissue matrix enclosed by a characteristic covering tissue, the germinal epithelium. It is in the latter tissue that the female gametes are first localized as distinct cellular bodies; the primordial female germ cells. (Plate XVI*C*,*D*.)

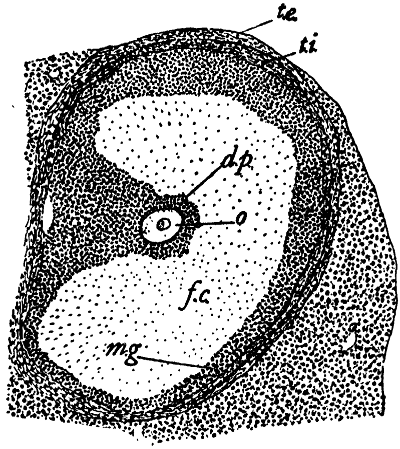


FIG. 169.—Portion of a section through the mammalian ovary (white rat) showing a nearly mature Graafian follicle with egg as it appears under the microscope. *d.p.*, discus proligerous; *f.c.*, follicular cavity; *m.g.*, membrana granulosa; *o*, ovum, or egg; *t.e.*, *t.i.*, outer membranes. *Cf.* Figs. 60, 170. (*Wieman.*)

During the years of sexual maturity, the immature primordial germ cells continuously migrate from the outer germinal epithelium centrally into the peripheral matrix of the ovarian tissue where each forms a Graafian follicle. The latter is first seen as a tiny spherical area in the matrix containing a comparatively large central cell; the immature egg or oögonium, surrounded by one or more layers of follicle cells. In the functional mature ovary, numerous Graafian follicles of various sizes and stages of development are found scattered through the connective tissue matrix. As the egg cell passes through

the various developmental stages, it gradually increases in size, but even more the size of the entire follicle increases until it becomes a large fluid-filled cavity bounded by several layers of follicle cells and containing the large egg cell, now known as an *oöcyte,* mounted as if on a pedestal (discus proligerus) of follicle cells; several layers of these cells also enclose the oöcyte. (Fig. 169.)

Though the germ cells first migrate into the ovarian tissues and give rise to tiny Graafian follicles, the great increase in the size of these structures, as the gametes approach maturity, brings them not only to the periphery of the ovary again, but they actually bulge

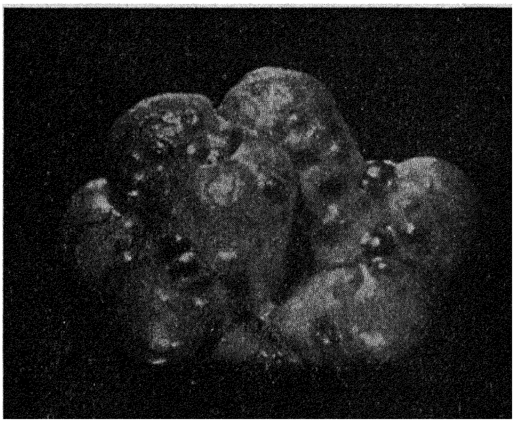


FIG. 170.—Photograph of a normal pig ovary showing numerous small transparent elevations, each of which is a Graafian follicle with an egg, and also several large opaque spherical bodies which are the corpora lutea and mark the sites of previous Graafian follicles. (*Cf.* Figs. 60, 169.) *Allen, "Science in Progress," Yale University Press. After Allen, Kountz, and Francis.)*

out from the surface as transparent, blister-like areas, plainly visible to the naked eye. When the enclosed egg cell is fully mature and ready for release from the ovary, it breaks directly through the surrounding layers, follicle cells as well as the outer germinal epithelium of the ovary, at the most convenient spot. During this period of development in a follicle, profound changes are occurring in the nucleus of the gamete that insure the proper maternal heritage to the zygote. This basic feature of gamete formation will be discussed in the next chapter. There is no direct connection between ovary and oviduct as there is between testis and sperm duct; and though the opening of the oviduct lies in close proximity to the ovary, there is always the chance that an egg liberated from the ovary may fall into the abdominal cavity instead of passing into the oviduct.

The two hormones, estrone and progesterone, produced in the ovary have already been discussed in the chapter on Secretion (page 116). Particular attention should be called to important ovarian endocrine tissue, the corpus luteum, which develops in the cavity of a follicle shortly after ovulation occurs, apparently from the follicle cells that

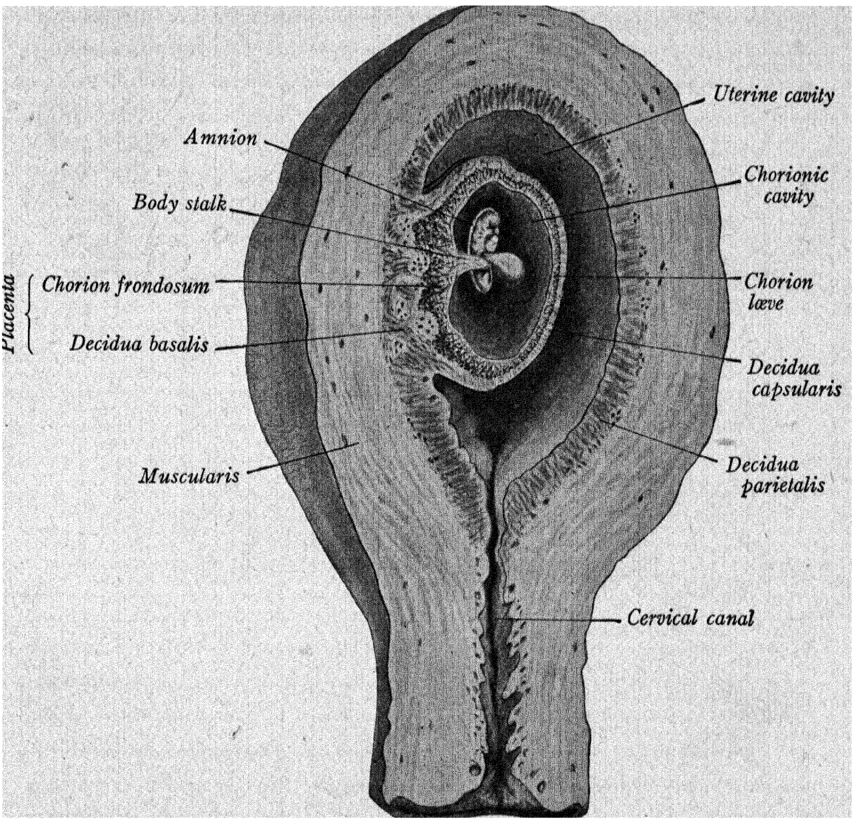


FIG. 171.—Section of a gravid human uterus showing five weeks embryo and associated structures. Diagrammatic. (*Arey, "Developmental Anatomy," W. B. Saunders Company.*)

remain *in situ*. The amount of the corpus luteum tissue formed and the period of its retention as a functional glandular tissue depends upon the fate of the egg. If the egg is not fertilized, the corpus luteum soon begins to decrease in size, and, shortly, only scar tissue remains in the ovarian wall to mark the location of the follicular area. On the other hand, if the egg is fertilized and development gets under way in the uterus, the corpus luteum continues to increase in amount for some time after ovulation and to secrete the powerful hormone pro-

gesterone which is responsible for the omission of ovulation and also for the cyclical menstrual changes during pregnancy. (Figs. 60, 170.)

The uterine development of the mammalian fetus necessitates marked structural and functional changes in the oviducts, which, in the lower types function merely as egg-conducting tubes. Thus the human oviduct is divided into three distinct regions: the oviduct proper, or fallopian tube; the uterus; and the vagina. The uterus and vagina are single, unpaired structures which develop from the union of the distal portions of the right and left oviducts. Each oviduct in the human female is a very small tubular organ about 4 in. in length and with a tiny central cavity, or lumen, about the size of a bristle. It is lined with ciliated epithelium which aids in the movement of the

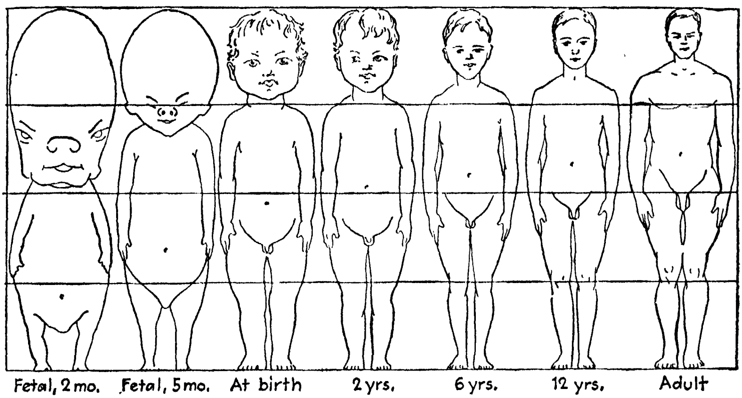


FIG. 172.—Changes in human body proportions during prenatal and postnatal periods. (*Sherbon, after Stratz.*)

eggs toward the uterus. The sperm apparently swim against the ciliary current in passing up the oviducts to fertilize the eggs. The walls of the uterus are largely composed of unstriated muscle tissue which is covered on the outside with the peritoneal epithelium and lined with a vascular mucous membrane. The cavity of the uterus is, of course, continuous with the lumen of the oviducts. Functionally, the uterus is characterized by its great extensibility during pregnancy when it may increase from approximately 3 in. to 1 ft. or more in length in accordance with the size of the growing fetus. There is also great flexibility in the position of the uterus. It is not firmly attached to any bony structure but rather suspended, as it were, by a number of flexible ligaments which permit a shift in position in response to the various mechanical factors appearing during pregnancy. With the completion of uterine development, rhythmic contractions of the uterine musculature, under the influence of unknown factors, begin which,

in the course of a few hours, are usually powerful enough to force the embryo from the uterus and out through the vagina to the exterior; the process of childbirth. (Plate XVI*C*, *D*; Figs. 171, 172.)

Another characteristic of the mammalian uterus is a periodical series of changes in the lining tissues which are apparently essential to the proper preparation of the uterine wall for the imbedding and nourishment of the fertilized egg. In the lower mammals, these cyclical uterine changes occur once or twice a year and are known as the *period of heat,* or *oestrus.* In the human female, the menstrual periods normally occur every 26 to 28 days during the period of sexual maturity. The latter typically extends from about the twelfth year to forty-five or fifty years of age. As noted above, the menstrual

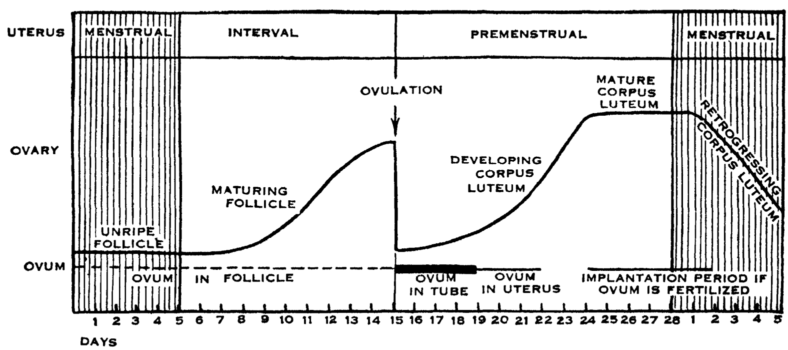


FIG. 173.—Scheme illustrating the ovarian and uterine cycles. (*Haggard, "Science of Health and Disease," Harper & Brothers.*)

phenomena do not occur during pregnancy. Each menstrual period is from 4 to 6 days' duration and is marked by a considerable discharge of blood from the uterine cavity which passes to the exterior through the vaginal opening. Histological examination of the menstrual discharges reveals the presence of numerous epithelial cells from the lining of the uterus. As a matter of fact, it is clear that menstruation is primarily due to a degeneration of the uterine lining with the consequent exposure of, and leakage from, the underlying capillaries. The tissue degeneration is followed by regenerative processes; and thus, periodically, a new lining surface is established in the uterus for the reception of the developing embryo. Primarily the menstrual phenomena are controlled by hormone action. The permanent cessation of menstruation at forty-five to fifty years of age indicates the end of ovulation and fertility. This period, known as the *menopause,* or *climacteric,* may be accompanied by certain definite clinical symptoms, such as varying temperature reactions, muscular pains, and dizziness.

In some cases, temporary psychical reactions of a more or less disturbing nature also appear during this change of life. (Fig. 173.)

The final structural unit derived from the oviducts is the vagina, which is an unpaired tubular structure extending from the uterus to the external opening or vestibule. Previous to sexual union, the external opening of the vagina is partially closed by a thin membranous sheet, the hymen. In the mammalian female, contrary to the condition noted above in the male, the genital organs have separate ducts and openings independent of those of the urinary system. The clitoris, a small unpaired organ with erectile and nerve tissue, homologous in its development with the penis of the male, is situated anterior to the opening of the urethra. (Plate XVI*D*).

The immaturity of most mammalian embryos at birth makes it necessary for the infant to be nourished by the mother for some time. And, so, associated with the mammalian female reproductive system are one or more pairs of mammary glands for the formation and secretion of a nutritive fluid, milk, which is adapted for the infant nutrition. The single pair of mammary glands,[1] or breasts, of the human female are small during childhood; but at the time of puberty, they begin to enlarge as a result of the growth of the associated connective tissues together with the deposition of fat. The glandular function, however, remains inactive until pregnancy occurs. During gestation, the glandular tissues show a further gradual increase in size and, under normal conditions, are ready for functional activity following childbirth. (Fig. 51.)

[1] Consult Appendix: Mammary Glands.

CHAPTER XIII

THE BIOLOGY OF GROWTH AND REPRODUCTION (II)

In the chapter just preceding, general consideration was given to the basic features of plant and animal reproduction, and, with this material as a foundation, a rather complete description was presented of the reproductive processes in three representative vertebrates: the frog, domestic fowl, and man. It was emphasized that reproduction is not essential for the maintenance of the living state in the individual organism but is solely concerned with the perpetuation of a particular type of species through the production of new individuals that are true to type. The perpetuation of a species means that the new individuals

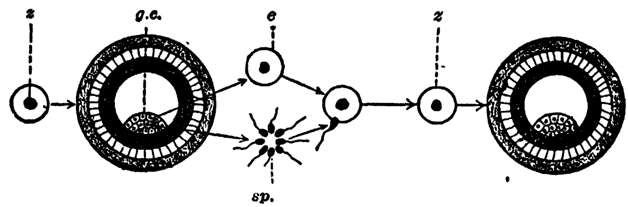


FIG. 174.—Scheme illustrating the reproductive cycle in a triploblastic animal with sexual reproduction in which only the sperm and egg bridge the generations and, therefore, necessarily carry the entire body of heritable materials. *e*, egg; *g.c.*, germ cells; *z*, zygote. (*Woodruff, modified from Hegner.*)

must conform closely to the characteristic pattern. Without at present going into the question as to just what constitutes a species, it is a matter of common knowledge that species breed true; figs do not produce thistles, nor do mice beget elephants. Thus, a fixity of species exists from generation to generation. At the same time, it is also commonly recognized that a certain amount of individual variation is always present among the members of a particular species.

With this situation in mind, it becomes evident that some mechanism must be operating in the specialized germ cells, bridging the generations, that makes certain that the new individuals develop true to the parental types. Possibly the presence of an intracellular mechanism of inheritance is not so clearly indicated in certain types of asexual reproduction as it is in the more involved processes of sexual reproduction, for, in the latter case, the entire body of heritable materials transferred to the individual of the next generation is necessarily carried by a microscopic sperm and egg. (Fig. 174.)

On the other hand in asexual reproduction in the unicellular organisms where reproduction is by binary fission, or in the multicellular organisms where the processes of regeneration lead to the production of new individuals through the gradual growth and differentiation of considerable portions of the parent individual, it seems reasonable to expect that an offspring would conform closely to the parental individual from which it sprang. Nevertheless, even a superficial knowledge of the material at hand makes it evident that, in the absence of a basic intracellular mechanism, every cell division would offer almost unlimited opportunity for divergence in the daughter cells.

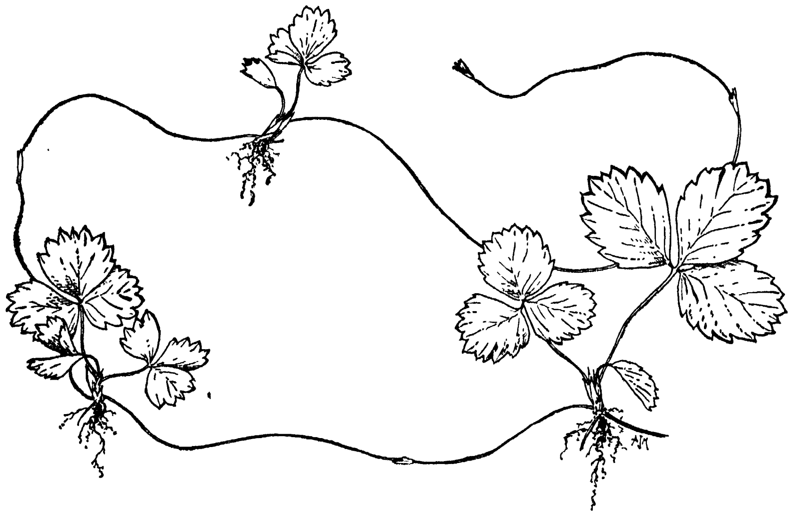


Fig. 175.—Asexual reproduction of the strawberry by the production of runners which later die away, thereby isolating a new plant developed directly from the parent. (*Haupt.*)

The fact of the matter is that whenever a cell undergoes normal division, or mitosis, be it plant or animal, soma or germ, the inheritance of the daughter cells is rigidly and accurately determined. From the zygote to the adult, mitosis is not a haphazard process. It is because of this fact that species do breed true and that the reproductive mechanism in any particular species of plant or animal operates to perpetuate that particular species and no other. (Fig. 175.)

Accordingly, it may be regarded as established that the production of a new individual of a particular species, whether asexually or sexually produced, is always dependent upon the orderly processes of mitosis and, though occasionally something may go wrong and a freak or monster may appear, it is a matter of common observation that abnormalities are so rare as to cause the widest interest. The descrip-

tions of various species by the earliest systematists, if based on accurate observations, check absolutely with the individuals of the same species living today, though in the meantime untold generations have come and gone. Or we may go back far, far beyond the time of even the earliest systematist and compare the structural characteristics of various plant and animal types, which lived millions of years ago, with their descendants now living and still occupying their particular niches in the amazing web of life.

But turning to the other side of the picture, lest the principle of the fixity of species be overemphasized and thereby the impression given that all species have remained essentially unchanged throughout the previous ages, it should be stated at once that plenty of evidence exists also to show that species have changed at various times in the past and that further changes may still occur. There is descent with change; a basic relatedness occurs throughout the living world that gives evidence that in the beginning there was a common life stream from which all the infinite varieties of organisms now present in the world of life, as well as a great many types that have entirely disappeared, have been derived. Biologists are convinced that the intracellular mechanism associated with the mitotic phenomena in cell division is primarily responsible for the production, generation after generation, of offspring conforming to the species type; for the individual variation that is apparent with the members of a species; and, finally, for descent with change, or, as it is more commonly termed, *evolution.* With the explanation of these basically important features bound up with mechanism of cell division, it is obvious that a thorough understanding of all phases of this basic process is necessary.

MITOSIS

Mitosis is primarily a nuclear phenomenon involving an exact division of the chromatin; the essential substance for the transfer of the heritable materials to the daughter cells. In the accomplishment of this central aim the nucleus temporarily disappears and an elaborate apparatus, the spindle, is temporarily set up in the cell cytoplasm so that the entire cell is involved in the complicated mitotic phenomena. Although mitosis is normally a continuous process from the time it begins until the single cell has divided to form two cells, four stages during the process are generally recognized, namely, prophase, metaphase, anaphase, and telophase, to which consideration may now be given. (Fig. 176.)

The Prophase.—Just previous to the beginning of the prophase, the nuclear and cytoplasmic elements in a cell appear in their normal

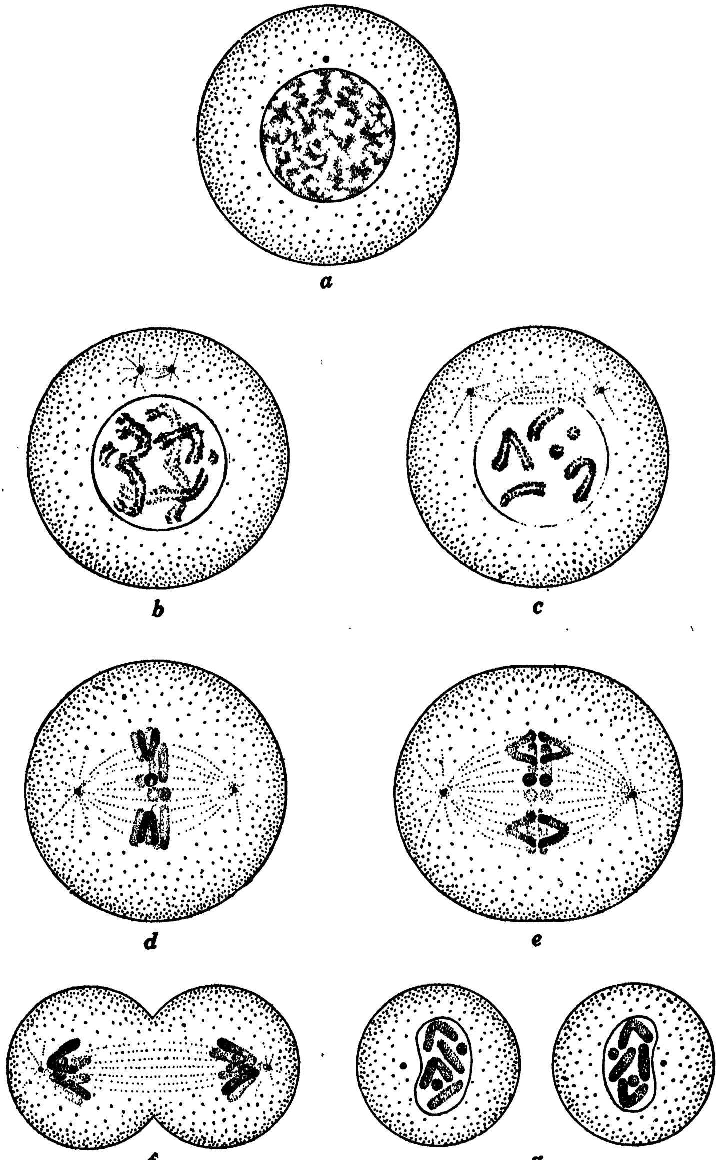


FIG. 176.—Diagrams illustrating important stages in mitotic cell division. *a*, cell in resting stage; *b*, *c*, beginning of cell division indicated by division of the centrosome lying above the nucleus and the condensation of the chromatin to form definite chromosomes (prophase); *d*, equatorial plate stage (metaphase) with first cleavage spindle well formed and division of each chromosome into two parts; *e*, separation of the halves of each chromosome and beginning of migration to the opposite poles of the spindle (anaphase); *f*, final stage (telophase) just previous to the separation into daughter cells, as shown in *g*. (*Watkeys, Stern, modified.*)

structural relationships; but as this stage develops, marked changes in the structural pattern are in evidence as the cellular materials are rearranged for the approaching climax of cell division. The beginning of the prophase in animal cells is first indicated by the activity of the centrosome, a very minute particle in the cytoplasm, lying in close contact with the nuclear membrane, which splits into two daughter centrosomes. The latter, without delay, begin to move away from each other toward the opposite poles of the cell. Each of the centrosomes is quickly surrounded by a structurally modified region of the cytoplasm from which fibrils, or rays, soon radiate peripherally to form the aster. As the two centrosomes with their surrounding astral halo continue to move apart, numerous fibers of another type appear in the cytoplasm between them. These are the spindle fibers, and they extend from each centrosomal area toward the center of the cell where they join with the nuclear elements and thus form a fibrillar spindle. The center of the spindle is approximately in the center of the cell where it surrounds the nuclear area. During the peripheral migration of the daughter centrosomes and the development of the asters and the spindle, profound changes have been occurring in the nucleus. Externally, this is marked by the gradual disappearance of the nuclear membrane, thereby removing the boundary between cytoplasmic and nuclear elements. (Fig. 176*a*, *b*, *c*.)

But of greater importance in the transfer of hereditary characters is the decisive rearrangement of the chromatin pattern marked by the development of definite structural units, the chromosomes. At the beginning of mitosis, the chromatin throughout the nuclear area appears as an irregular network with embedded particles of various shapes and sizes. Soon this is changed, and the chromatin is consolidated to form a definite number of long thread-like bodies, the chromosomes, which with the proper technique are beautifully differentiated in stained preparations and can also be seen in living cells under certain conditions. Expert examination of a chromosome under the highest magnification shows that it is essentially a double structure with two chromatin elements in close contact, or fused, throughout their length. As a matter of fact, the double condition of the chromatin is usually apparent in the early prophase stage. Furthermore, it is apparent that all the chromosomes do not have exactly the same shape but exhibit a distinct structural individuality; some are long, some short, some angular, some like tiny spheres. This individuality of the chromosomes has deep significance and will be considered later in connection with the development of the germ cells. The formation of the specific chromosome entities from the apparently nondescript

net-like chromatin and their attachment to the spindle fibers mark the end of the prophase.

The Metaphase.—This stage of mitosis is a comparatively short one. It is characterized by the definite alignment of the chromosomes in the center, or equator, of the spindle, equidistant from the two asters. This region of the spindle is termed the *equatorial plate*. The mechanics involved in the shifting and definite arrangement of the chromosomes in the equatorial plate are quite obscure, but, presumably, forces applied through the attached spindle fibers are responsible. At all events, the underlying plan is evident, for the chromosomes are thus placed in the proper position for longitudinal cleavage, which occurs during the next stage of mitosis, the anaphase. (Fig. 176*d*.)

The Anaphase.—The anaphase may, perhaps, be regarded as the climax of mitosis for during this stage, as just stated in the preceding paragraph, each of the chromosomes in the dividing cell splits longitudinally to form two chromosomes. This longitudinal division separates the two elements of the double chromosome structure, noted in the prophase stage, in a precise qualitative and quantitative manner so that each of the two resulting cells receives the correct chromatin content. The two "daughter" chromosomes, formed by the division of each of the chromosomes in the equatorial plate, now move in opposite directions toward the aster from which the attached spindle fibers radiate. And so, when cell division is completed and two independent cells have been formed, it will be found that the nucleus of each of these cells does not contain a miscellaneous array of chromosomes but always one chromosome from each pair formed by the splitting of the chromosomes, as just noted. Since it was apparent in the prophase stage that a chromosome is a double structure, it may be simpler to say that, during the anaphase, the two elements of each chromosome undergo complete separation and move toward opposite poles of the spindle. (Fig. 176*e*.)

The forces involved, both in the longitudinal splitting and in the later separation of the half-chromosomes during the anaphase, are by no means fully determined as, indeed, is the case with most of the mitotic phenomena, but considerable evidence is now at hand to show that the chromosome elements are actually pulled apart as a result of the contraction of the attached spindle fibers. To visualize this process, it is necessary to assume that the spindle fibers from each pole of the spindle extend only to the equatorial plate, where they are directly connected with the chromosomes in such a way that the pull exerted by a contraction of the spindle fibers will separate the two elements of each chromosome and draw each half toward the aster from which the

particular group of spindle fibers extends. The continued movement of the daughter chromosomes away from each other and toward opposite poles of the spindle is even more difficult to explain. Apparently no visible evidence exists that would indicate a pull on them as a result of continued spindle fiber contraction. Nevertheless, the polar movement of the two chromosome groups continues so that, as the anaphase stage ends, they are widely separated, with each group lying in close proximity to the corresponding aster. Evidences of the route travelled from the equatorial plate are seen in an orientation of the cytoplasmic elements parallel to the direction of chromosome movement.

The Telophase.—This end phase of mitosis is characterized by a number of structural changes in the elements of the dividing cell. Externally a prominent feature in animal cells is the formation and gradual development of a cleavage plane that first appears as a slight depression in the cytoplasm at the equator of the cell. This may be seen to excellent advantage in the holoblastic cleavage of the fertilized egg, such as previously described in the frog. The continued ingrowth of the cleavage furrow finally results in the division of the cytoplasm of the original cell into two daughter cells. The internal nuclear changes made evident by a microscopic study of cells in the telophase stage reveal the final chapter in the mitotic phenomena previously traced through the prophase, metaphase, and anaphase stages. Outstanding is the reappearance of the nuclear membrane and also of that functionally obscure body, the nucleolus, in each of the daughter nuclei. (Fig. 176*f*.)

Along with these altered features is a change in the appearance of the chromosomes. They begin to lose their clear visibility and gradually merge into the irregular, granular network present in the nucleus of the parent cell at the beginning of the prophase stage. Accordingly, so far as can be seen under the microscope the chromosomes appear to be temporary chromatin bodies which reach their highest development in the metaphase and anaphase and gradually disappear during the telephase. They will not become prominent again until the daughter cells undergo mitosis. However, it must not be thought that the basic chromatin organization disappears in a resting nucleus or that it is in any sense haphazard; for whenever the chromosomes reappear in the cells during succeeding mitoses, the exact number and shapes that were present in the ancestral cells again "crystallize" out of the chromatin net. Finally, in each daughter cell a gradual disappearance of both the astral fibers and spindle fibers radiating through the cytoplasm is evident, and the tiny centrosome,

shorn of its astral halo, once again lies close to the nuclear membrane, ready to divide and thus inaugurate the prophase of the next mitosis. Successive mitoses usually follow each other in rapid succession in the early stages of embryonic development, and the successive generations of daughter cells get smaller and smaller, as can be seen in the blastula and gastrula stages of the frog embryo. In the more mature cells, however, long inactive periods normally follow the completion of mitotic activity. In fact, many highly differentiated types of cell completely lose the power of mitosis in the adult.

Thus ends the amazingly exact process of mitosis on which the integrity of successive generations of cells and, in the final analysis, of every organism depends. The fertilized egg cell contains its exact quota of maternal and paternal chromatin, and, during the successive cell divisions essential to the attainment of the adult stage, every daughter cell receives its rightful share of the chromatin legacy established in the zygote nucleus. And so it is apparent, as stated in the first chapter, that "cell division is an exquisitely beautiful and exact process (page 13). On its normal functioning during all the stages of embryonic development and throughout the life of each individual depends the structural and functional integrity of every tissue and organ of the body, as well as the specific characteristics of the entire organism."

CHROMOSOME STRUCTURE

Since the entire process of mitosis hinges on an exact division of all the chromosomes so that the nucleus of each daughter cell may receive its rightful share of every chromosome, it is apparent that the hereditary materials in the chromosomes must be arranged with the utmost regularity and precision. Without, for the moment, bringing forth the available experimental data, it may be stated that there is abundant evidence demonstrating that every chromosome, whether present in the nucleus of a body cell or in germ cell, is composed of a great many independent ultramicroscopic hereditary units, the genes, which are arranged in a precise linear fashion throughout the length of the chromosome. It is well established that some 2,500 genes are present in certain chromosomes of the fruit fly Drosophila, which are responsible for the control of various hereditary characters. In addition, it has been found possible to secure data from various controlled breeding experiments in this organism that indicate the positions of many of these genes in a particular chromosome. In this way, chromosome maps have been constructed that indicate the gene loci. (Fig. 181.)

With this linear arrangement of the gene-chromosome complex in mind, it is evident that, when a chromosome reproduces and splits in half longitudinally, each of the constituent genes, linearly arranged throughout its length, also reproduces and splits. Thus each of the daughter chromosomes receives its share of every gene present in the parent chromosome. The assemblage of a complete set of the daughter chromosomes in the nucleus of each daughter cell transmits the complete gene heritage of the dividing cell. In a word, then, the nucleus of a daughter cell is exactly like that of the parent cell except that, at the instant it is formed, it is only one-half the parental size. The cell cytoplasm simply splits into halves, but this relatively crude method cannot be used for the chromatin material in the nucleus inasmuch as every one of the untold thousands of genes must undergo exact qualitative and quantitative division if the normal inheritance pattern is to be transmitted.

The daughter cells having been formed, the next event is an increase in the amount of both cytoplasm and of the chromatin until the normal cell size is once more reached. Growth takes place during the period in which a cell is inactive mitotically. In such a condition, as shown in the prophase at the beginning of mitosis and again at the conclusion of the telophase stage, the chromosomes are not found as microscopically visible bodies. During the growth period, new chromatin material is being formed and added to that already present in the nucleus. In some way, not understood at present, this process is so exactly controlled that, when the chromosome structure is again rebuilt out of the irregular network of the resting cell, every chromosome reappears with its individual structural characteristics and with every gene in its exact spatial relationship and containing its own specific hereditary substances.

It has just been shown that the number of chromosomes and their exact structural and functional features pass unchanged through successive cell generations. To take a specific example, if a fertilized egg cell has 48 chromosomes, as in Man, every one of the trillions of body cells in the adult individual will have 48 chromosomes. Furthermore, the 48 chromosomes present in the last cells formed during embryonic development, whether differentiated as epithelial or vascular or nerve cells, will have the exact structural pattern of the original 48 chromosomes in the fertilized egg. Again, every individual belonging to the human species will be found to have 48 chromosomes of the same type, no matter where he lives or what his nationality or race happen to be. This condition is only what is to be expected if, as we know, the composite characteristics of an organism are the

"outcropping" of the gene complex established in the fertilized egg. Or, stated in another way, individuals that exhibit the same characteristics, so that they are placed in a single species, will have the same chromatin complex as shown by an exact uniformity in the number and type of chromosomes. A microscopic examination of the chromosome patterns of even closely related species, for example those of the horse

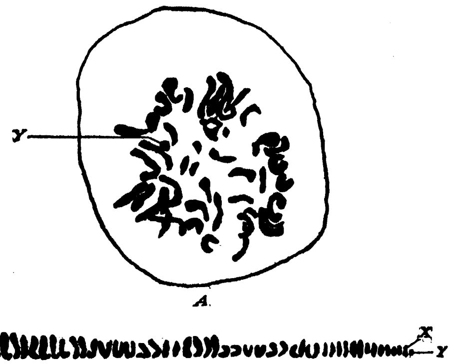


FIG. 177.—The chromosome complex in man. *A*, the normal chromosome pattern; *B*, the arrangement of the chromosomes by pairs. (*Painter, "Eugenics, Genetics, and the Family," The Williams & Wilkins Company.*)

and the ass, reveals distinct differences. Possibly all this is only a rather involved way of emphasizing the fact that every type of organism has its own distinctive gene complex, and variations in these are apparent to the cytologist in the numbers and shapes of the chromosomes. (Figs. 177, 220.)

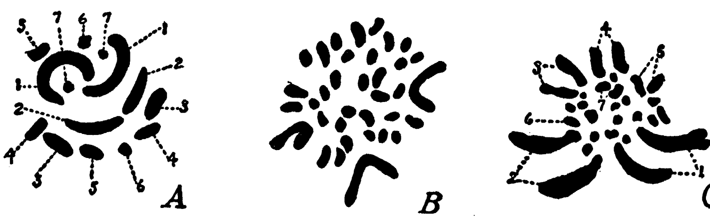


FIG. 178.—Illustrating the individuality of the chromosomes. *A*, chromosomes of a plant louse. The homologous chromosomes are given the same number. *B*, chromosomes of a beetle; *C*, chromosomes of a seed plant. (*Wilson.*)

During the present century and even before, a great deal of intensive research work has been done by the cytologists on the chromosome patterns of many species of plants and animals. The accumulated data show that wide variation occurs in the different species both with respect to the number of chromosomes and their distinctive structural features. In a particular species, however, as emphasized above, the

chromosome complex (karyotype) is always constant. The results from the chromosome studies have yielded important evidence with regard to the degree of relationship among various types. Thus, to take one important example, from a study of the chromosome patterns of several different species of Drosophila, it is evident that all the specific patterns "bear a general resemblance to one another but show characteristic minor differences." Since the various species of Drosophila present in a particular genus show specific differences, it is to be expected that the karyotypes of these same species would also show minor differences. But the impression must not be given that the structural pattern of the chromosomes can be directly associated with the morphology of the individual or, in other words, that it would be possible by a study of the chromosomes in a fertilized egg to arrive at any conclusion relative to the characteristics of an organism developing from such a complex. Such is not the case. Nor is there any apparent relationship between the number of chromosomes and the relative complexity of an organism. (Fig. 178.)

Fig. 179.—The normal diploid chromosome complex (karyotype) of the fruit fly, *Drosophila melanogaster*. (*Sharp, adapted from Morgan, Sturtevant, Bridges, and Stern.*)

Inasmuch as the more complex organism possesses a greater number of characteristics to be determined than does a relatively simple organism, it might be expected that the former would have more determiners, or genes, for these characters and, therefore, that the chromosome number would be larger. It is found, however, that some of the highest chromosome counts are in the Protozoa, whereas

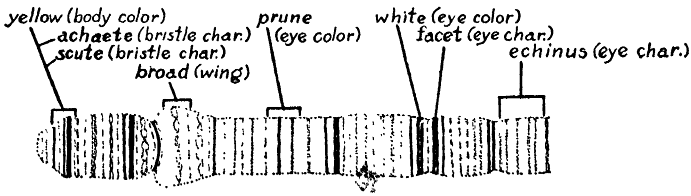


Fig. 180.—Drawing of a terminal portion of a giant X-chromosome from a salivary gland cell of Drosophila to show the position of certain genes which determine body and eye color and other characteristics of wings and bristles. *Cf.* Figs. 181, 183. (*Painter, "Science in Progress," Yale University Press.*)

Drosophila, a highly developed invertebrate, has only eight chromosomes. It is possible, however, that the eight chromosomes in the Drosophila karotype contain many more genes than do the much more numerous chromosomes of the protozoan cell. It is apparent that chromosome number is far too coarse a measure to use in establishing a direct relationship between chromatin structure and body

structure. If the genes themselves were large enough to be directly studied under the microscope, just as we can now study the chromosomes, undoubtedly structural features in the organism could be directly associated with the structure pattern in a particular gene or group of genes. It has been previously stated that it has been found possible in a few organisms to determine the definite region in a particular chromosome in which the genes responsible for certain bodily structures are situated and thus to make a chromosome map. These results, as will be shown later, were first obtained by breeding experiments in Drosophila, but it has been possible to confirm them by direct microscopic observations on the chromosomes. Within the last few years, it has been discovered that the salivary glands of Drosophila contain cells bearing relatively enormous *giant chromosomes* in their nuclei. Intensive microscopical studies on this material have brought the observations of the cytologist very close to actual gene visibility and have greatly added to our knowledge of the minutest elements of chromosome structure, in fact, the way the genes are actually arranged. We may now briefly indicate the minute structural pattern of chromosomes as shown by the study of the giant chromosomes from the salivary gland cells. (Figs. 179 to 182.)

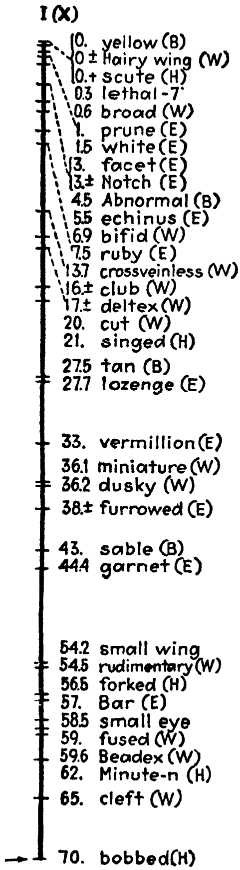


FIG. 181.—Showing the complete chromosome map as determined for the X-chromosome of Drosophila shown in Fig. 180. (*Sharp, adapted from Morgan, Sturtevant, Bridges, and Stern.*)

The giant chromosomes are elongated cylindrical bodies with more or less regularly spaced bands encircling them throughout their length. Their appearance under the microscope reminds one of an earthworm with its segmented body indicative of a characteristic internal arrangement of the various parts. In the same way, the external segmentation or banding of the chromosomes presents visible evidence to the microscopist of a definite arrangement of the genes or at least of the regions, or "homes," that they inhabit. For each external band of a chromosome marks the outer boundary or periphery of a disc-like structure lying at right angles to the main axis of the elongated chromosome. Certain evidence goes to show that the actual genes

are grouped in these disc-like bands throughout the length of the chromosome. There seems to be no question but that the genes, even in the giant chromosomes, are somewhat too small to be seen under the highest magnifications. (Fig. 183*a*, *b*, *c*, etc.)

Fortunately the giant salivary gland chromosomes, when prepared and stained in the proper manner, are essentially transparent, which makes it possible for the cytologist to study their complex internal arrangement. In such observations, the microscopist must make use of the highest magnifications available, and even then it is not possible to speak with absolute authority on the finest details of chromosome structure. The concensus of opinion at present seems to be that the typical giant chromosome is essentially cable-like in its structural pattern with a variable number of linear units, the chromonemata,

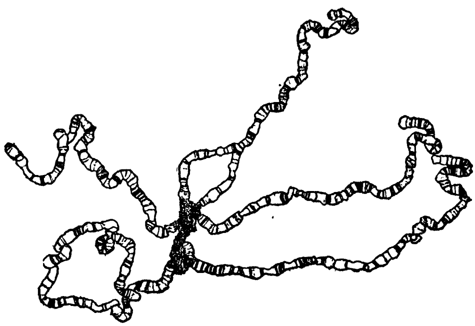


FIG. 182.—The entire group of giant salivary gland chromosomes of Drosophila. They are attached in the center to a granular material, chromocenter, which lacks genes. (*Shull, after Painter, modified.*)

spirally wound together to form the chromosome body. In the giant chromosomes, 64 chromonemata have been observed, but the number may be more or less. Embedded in the thread-like chromonemata, at rather regularly spaced intervals, are chromatin particles, the chromomeres, appearing like knots tied at more or less regular intervals in an elastic thread. The elastic threads are the chromonemata, and the simile appears to be unusually descriptive, for it is even possible to stretch the fresh salivary gland chromosomes and thus increase their length somewhat. Under such conditions, it is the chromonemata that are stretched, and this stretching increases the distances between the knot-like chromomeres present on the filamentous elastic chromonemata. (Fig. 183.)

Chromosomes, chromonemata, and the chromomeres, the latter being the smallest elements visible under the microscope—where are the actual genes, and how can the external banded areas be linked up with the internal structure as just given? The evidence is that the

genes are present in the chromomeres. The latter, as microscopically visible particles, are undoubtedly too large to be the actual genes, but they are believed to be essentially a chromatin covering which surrounds and encloses the genes. Finally, what is the relation between the chromomeres and the banded discs mentioned as the home of the genes in the preceding paragraph? This condition may perhaps be understood by saying that the chromomeres are concentrated in the disc-shaped areas. For sake of illustration, let us visualize the discs as many-roomed mansions and the chromomeres as private rooms inhabited by the genes. The chromonemata appear to be strung along like telephone wires from one "gene dwelling" to the next throughout the length of the chromosome.

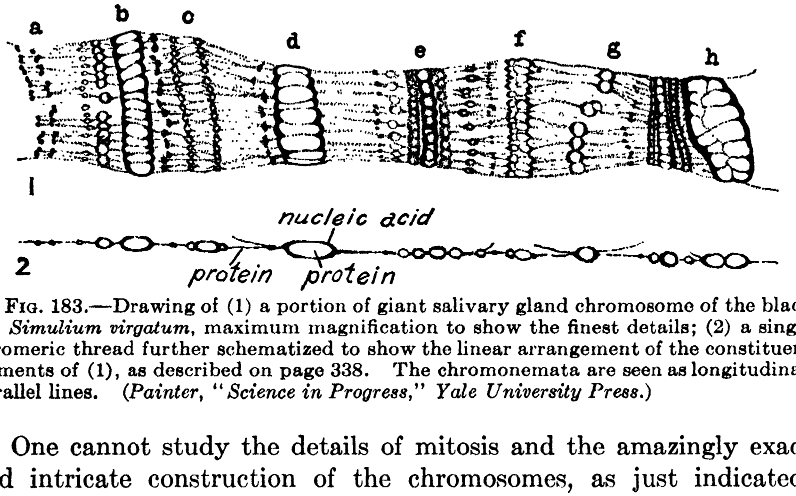


FIG. 183.—Drawing of (1) a portion of giant salivary gland chromosome of the black fly, *Simulium virgatum*, maximum magnification to show the finest details; (2) a single chromeric thread further schematized to show the linear arrangement of the constituent elements of (1), as described on page 338. The chromonemata are seen as longitudinal, parallel lines. (*Painter, "Science in Progress," Yale University Press.*)

One cannot study the details of mitosis and the amazingly exact and intricate construction of the chromosomes, as just indicated, without being tremendously impressed with the basic importance of these cellular elements. If an experiment were devised to show conclusively that the chromatin material is the basis of heredity, it would probably consist in transferring living chromosomes from the nucleus of one cell to that of another cell and then studying the effect of the transposed chromatin in the succeeding cell divisions. So far as can be seen at present, experiments involving the actual transfer of chromatin from cell to cell lie beyond the range of the experimental biologist, but, fortunately, data are available from experiments involving the same principles that are continually being performed in the greatest laboratory of all, the laboratory of nature, and by the greatest of all experimenters, nature.

In the past few years, numerous examples of chromosomal irregularities, or aberrations, have been discovered in well-known species of

plants and animals. In some of these, additional chromosomes have been added to the normal number; in other cases, the chromatin material has been reduced below that normally present. Now when the normal chromosome complex is altered, it is found that the individuals exhibit corresponding changes in various structural characters. Speaking very generally, it is found that, when the cells of an organism carry an increased number of chromosomes, the individual is larger in size and is also marked by other altered characteristics depending upon the gene content of the added chromosomes. Thus fruit, flies have been found with a 50 per cent increase in the chromosome number so that there were 12 chromosomes in each cell instead of the normal number of eight. Such animals are larger and show other modifications of the normal species pattern. Many other instances have been found, more commonly among plants, and, always, the results of altered chromatin pattern are evident in the individual. Some of the important results obtained in this field will be considered in the next chapter in dealing with problems of heredity. (Fig. 184.)

In spite of the fact, as noted above, that the biologist is decidedly limited in his ability to experiment with chromosomes directly, it has been found possible to make use of the X rays in altering the normal chromosomal pattern of the living cells. Some years ago, it was discovered that irradiation of the living male germ cells undergoing development in the testis of Drosophila caused decisive changes in the chromatin pattern of these cells so that later, when the sperm developing from these irradiated gametes were used to fertilize eggs, a considerable proportion of the resulting offspring were found to show various abnormalities, or mutations. Microscopic examination of the chromosomes from the mutated animals revealed visible changes in the chromosomes. These epoch-making results from irradiation, which have widely extended in various plant types, once more confirmed the basic fact that altered chromatin means an altered heredity in the daughter cells and the establishment of visible modifications in the cells, tissues, organs, and organism formed from the mutated cell or cells. (Fig. 207.)

Finally, it is established that the characteristic differences between male and female are definitely associated with what appears to be, from the structural standpoint, very slight differences in the chromosome complex of the two sexes. Almost forty years ago, it was found that all the body cells of the females in a certain species of insect had a pair of chromosomes that were visibly different from those present in the body cells of the males. In tracing this sex individuality back

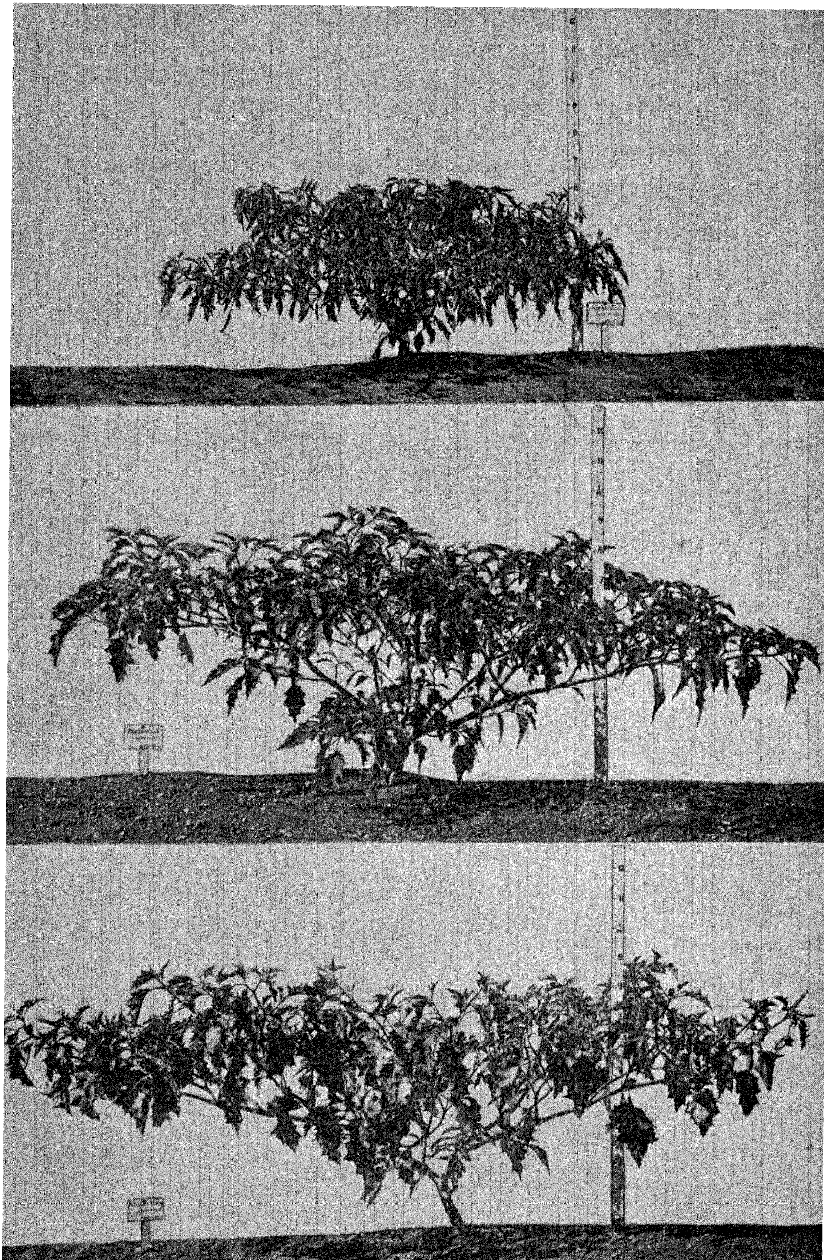


Fig. 184.—Photographs of the jimsonweed (Datura) with different chromosome complexes, as follows: Above, haploid; middle, diploid; below, tetraploid. (*Sinnott and Dunn, after Blakeslee.*)

to the chromosomes of the germ cells, it was found that all the mature eggs contained one sex chromosome of the same type, which we may designate as X, but that the sperm were equally divided between two types; one with an X chromosome, as in the eggs, and one with another type, known as the Y chromosome. Union of an egg with an X sperm gave the X-X pattern in the zygote, and this would develop into a female; fertilization with a Y sperm gave the X-Y pattern in the zygote which resulted in a male individual. Further consideration of this question will better be deferred until later, but the important point has been established, namely, that even the characteristic differences between the male and female have their origin in a distinctive gene pattern. (Fig. 179.)

GERM CELL FORMATION

The description of reproduction and chromatin behavior in the body cells, based upon mitosis, has been presented in sufficient detail so that we may turn to another and, possibly, even more important phase of reproduction, namely, germ cell formation. To get the essential background, it will be desirable to recall for a moment the early stages of embryonic development as described in the previous chapter (page 295). It was shown there that repeated cleavages extending through the blastula stage result in the formation of a considerable number of cells, all belonging to the ectoderm, the first of the primary germ layers. Then the gastrula stage appears, characterized by the development of endoderm cells. A little later, mesoderm cells are differentiated. Thus, cellular differentiation appears among the constituent embryonic cells, all of which are direct descendants of the original zygote. What is responsible for this differentiation, the appearance of which, in cells with the same chromosome complex, seems to argue against the chromosome basis of heredity as discussed in the earlier pages of this chapter? The answer seems to lie in minute changes occurring in the chromatin of the daughter cells; changes too small to be visible under the highest magnifications. Thus the most searching examination of the nuclei of ectoderm, endoderm, and mesoderm cells reveals no differences in the structural pattern of the chromosomes of the different types of cells, but undoubtedly ultramicroscopic differences are present in the gene complex, possibly extending down to the molecular level. The apparent uniformity of the mitotic phenomena really masks an inherent ability to segregate specific differentiating materials to particular cells during development. This segregation is the basis of the gradual and orderly processes of differ-

entiation which assume such amazing proportions in vertebrate animals. (Fig. 155.)

The differentiation processes during development result in the formation of the six basic tissues of the vertebrate organism, namely, epithelial, supporting, vascular, muscle, nerve, and reproductive (page 23). Various combinations of these tissues are responsible for the formation of the organs and organ systems that unitedly form the functioning organism; and all of them, with the exception of the reproductive tissues, are concerned with the maintenance of the structural and functional unity of the individual organism. Together

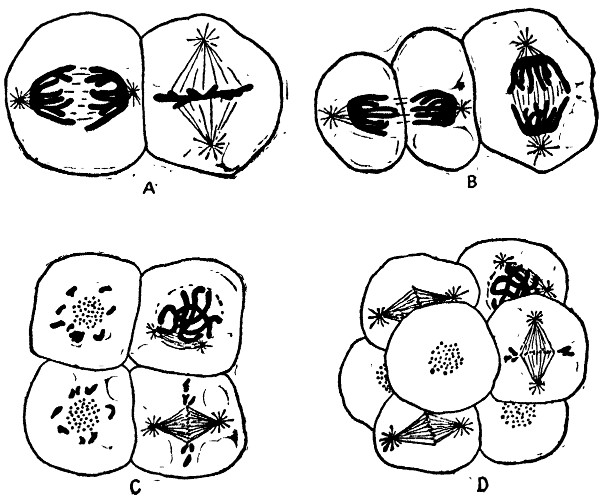


Fig. 185.—Diagrams illustrating the early differentiation of somatic and germ cells in *Ascaris megalocephala* during the cleavage of the egg. Germ cells at *right* in *A*, *B*; *upper right* in *C*, *D*. Schematized. (*Shull, after Fogg.*)

they comprise the *soma* of the individual that houses the *germ plasm* and, as a matter of fact, make it possible for the germ plasm to survive and to function in reproduction, thus maintaining the species. The time at which definite germinal cells are first segregated during embryonic development varies widely in the animal kingdom. Thus in the parasitic worm Ascaris, which supplies such important material for the study of the mitotic phenomena, the first cleavage of the zygote reveals differences in the nuclei of the two daughter cells, and it is established that the descendants of one of these two cells will form the germinal cells. In most species, visible differentiation between soma and germ plasm does not occur until very much later in development. (Fig. 185.)

But whether it be early in development or later, the main point is that in the individuals of species that reproduce sexually, differentia-

tion of germinal material occurs, and the germ cells thus formed pass through a series of developmental stages, the process of gametogenesis, which ends in the formation of the mature gametes, eggs or sperm. Gametogenesis may conveniently be divided into spermatogenesis and oögenesis in correspondence with the type of gamete produced. The basic features of germ cell maturation, involving the exact preparation of the chromatin material for transfer of hereditary characters to the next generation at the time of fertilization, are the same in the male cells as in the female, though as we know, from the description given in the preceding chapter, the structural features of mature sperm and egg are markedly different.

The heart of sexual reproduction is fertilization, and the essential feature of fertilization is the fusion, or amphimixis, of the chromatin material in the nucleus of the male sperm with that present in the nucleus of the female egg; thus forming the fusion nucleus, or synkaryon, of the zygote. Since we know that the characteristics of the daughter cells formed by mitosis depend upon their receiving the normal chromatin complex from the parental cell, it is no less apparent that, in reproduction, the integrity of the new individuals depends upon receiving the exact inheritance of maternal and paternal chromatin at fertilization. With this condition in mind, it is clear that the zygote nucleus cannot possibly receive the normal chromatin content of the species if both the sperm nucleus and the egg nucleus transfer to it the full amount of chromatin material, for a doubling of the chromatin content, evidenced by double the usual number of chromosomes, would be bound to result. The upshot of the matter is, as has long been recognized, that, in spermatogenesis and in oögenesis, the chromatin material of each germ cell is reduced to one-half the normal amount, and this condition is visibly shown in an actual reduction of the chromosome number to one-half that found in any other cells of the body of that particular species. It may be stated very simply: A mature sperm or a mature egg contains only one-half the somatic number of chromosomes. As a result of this chromosome reduction, it is evident that when a sperm nucleus unites with an egg nucleus in fertilization, the chromosome number of the zygote nucleus is restored to the characteristic number and not doubled as it would be otherwise. (Fig. 186.)

Chromatin reduction in the germ cells, like chromatinic behavior in mitosis, is not a haphazard process but is so arranged that each mature germ cell will carry a complete set of genes for all the characters of that particular type of organism, though the chromosome number is reduced one-half. In order to understand how this is accomplished, it will be

necessary to reëxamine the normal chromatin complex in the nucleus of a body cell and see just what the condition is there. Careful studies on animal tissues have shown that the nuclei of every type of somatic cell and the nuclei in the immature germ cells, as well, always contain a double, or diploid, set of chromosomes. The chromosomes are in pairs; every chromosome has a mate which is an exact duplicate, or, as the cytologists say, a homologous chromosome. Thus, technically, instead of saying that Drosophila has eight chromosomes, it is preferable to say that it has four pairs of chromosomes or that the diploid number is eight. Also in Man, since the diploid number is 48, 24 pairs of chromosomes are present. The individuality of each chromosome is so marked that it is possible for the experienced

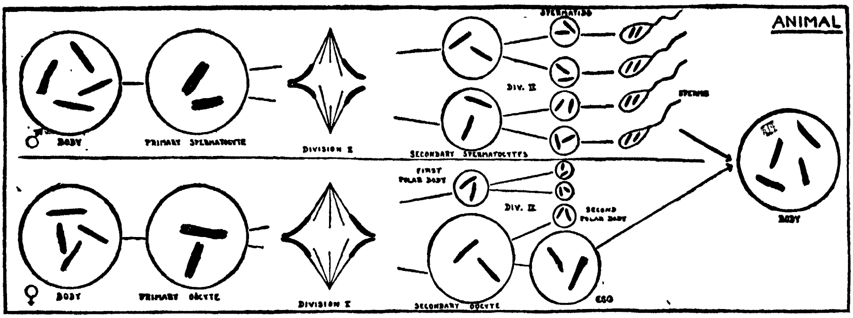


FIG. 186.—Illustrating the history of the chromosomes in the animal life cycle. Male, above; female, below; union of sperm and egg to produce the new individual, at the right. (*Sharp.*)

cytologist to identify the two members of each pair of homologous chromosomes. To do this is comparatively simple in cases like Drosòphila where only four pairs are present, but the chromosome identification presents considerable difficulty where numerous pairs are present as in man.

A moment's consideration will show that the essence of chromosome reduction during germ cell formation is the sorting out of one complete set of chromosomes, the haploid number, for transfer to each germ cell, whether egg or sperm. When the sperm carrying the paternal chromatin later unites in fertilization with the nucleus of the egg carrying the maternal chromatin, the synkaryon nucleus of the zygote is equipped with two complete sets of chromosomes, the diploid number, and, furthermore, the two homologous chromosomes of each pair present in the zygote have a diverse ancestry; one chromosome from each pair is of paternal origin by way of the sperm, and the other chromosome is of maternal origin by way of the egg. The successive mitotic cell divisions of the zygote, during embryonic development,

present to every cell of the body exact replicas of the paternal and maternal chromosomes received by the zygote nucleus at fertilization. Thus biparental inheritance, the unique characteristic of sexual reproduction, extends to every cell of the individual.

Spermatogenesis

With the general relationships between the chromatin of soma and germ plasm in mind, it is next in order to examine the process of germ cell formation and to find out just how these basic conditions for heredity are maintained. The development of the functional sperm may be considered first. The structural plan of the testis has been described in the previous chapter (page 315). It was there shown that the sperm are matured in the seminiferous tubules, the successive stages of development culminating in the production of free-swimming sperm which are liberated and pass from the tubules to the exterior. The problems involved in the morphological transformation of the early, or primordial, male germ cells, which appear as typical cells, to the bizarre motile sperm are of great complexity, but they are not of primary concern in this discussion for our interest lies in the behavior of the chromatin. Six characteristic stages of spermatogenesis merit our consideration; the first of these is the *primordial germ cell* which appears as a recognizable type at some period during embryonic development and is segregated in the seminiferous tubules of the testis. The early history of the primordial germ cells is essentially uneventful. They are small in size, but with a comparatively large nucleus containing the diploid number of chromosomes characteristic of the species. Repeated mitotic divisions of the primordial germ cells, the so-called multiplication period, results in the formation of great numbers of *spermatogonia* which are essentially the same in structure as the primordial cells, and in all of which exact and normal mitoses ensure the maintenance of the specific chromatin complex. (Fig. 187.)

The inauguration of the third stage in spermatogenesis is indicated by an increase in cell size; for after an indefinite number of divisions involving normal mitosis, each of the daughter spermatogonia enlarges to form a *primary spermatocyte*. Superficially, a primary spermatocyte appears as a greatly enlarged spermatogonium, but an examination of the nucleus reveals that the reduction phenomena, essential to germ cell maturation, are under way. Furthermore, it is found that a germ cell having reached the primary spermatocyte stage will divide only twice more; the first division forms two daughter cells designated as *secondary spermatocytes*, and then each of these divides

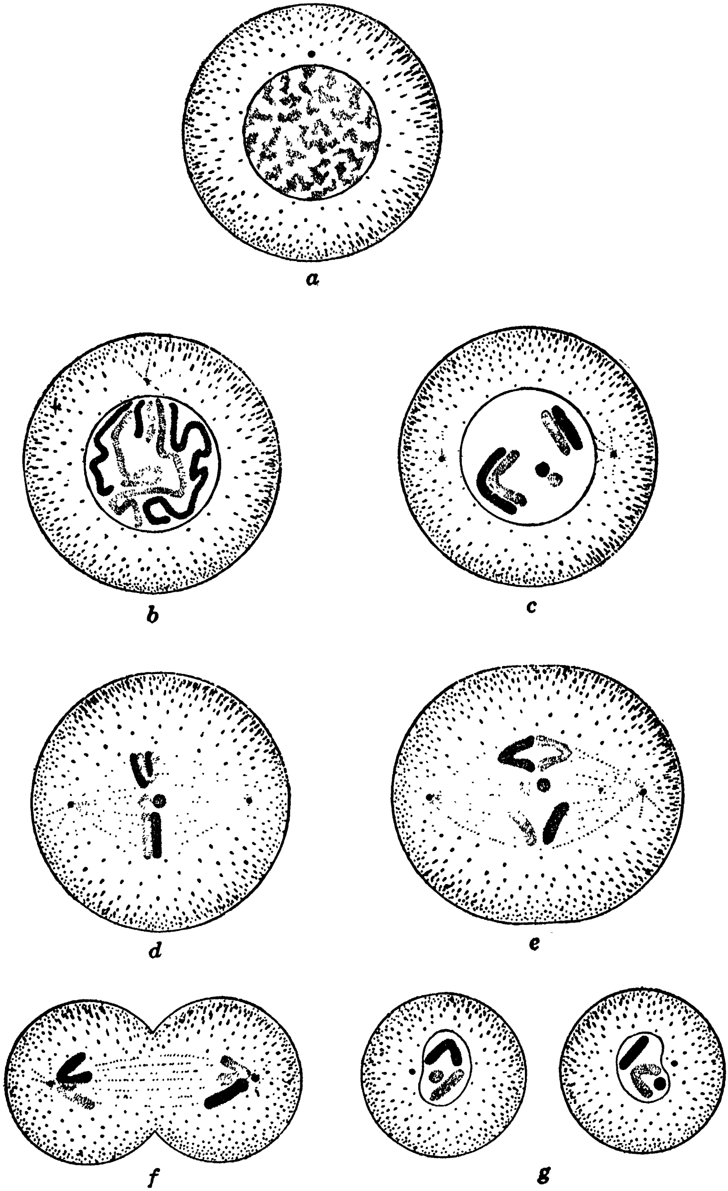


FIG. 187.—Diagrams illustrating meiosis during gametogenesis. *a*, diploid germ cell in resting condition; *b*, condensation of chromatin to form three pairs of homologous chromosomes; *c*, pairing (synapsis) of homologous chromosomes as in primary spermatocyte or oöcyte; (*d*), cleavage spindle in equatorial plate stage; *e*, *f*, separation of the homologous chromosomes and migration to opposite poles of the spindle; *g*, resulting daughter cells with reduced number of chromosomes as in a secondary spermatocyte or oöcyte. *Cf.* Fig. 186. (*Watkeys, Stern.*)

to form two *spermatids*. The spermatids, without further cleavage, are gradually transformed into mature *sperm*. In a word, then, the two final cell divisions beyond the primary spermatocyte stage result in the formation of four sperm from each primary spermatocyte. (Fig. 186.)

Synapsis.—In the previous description of mitosis, it was shown that the real crux of the process was the longitudinal splitting of each chromosome and the separation of the resulting halves in such a way that each daughter cell would receive one-half of each chromosome, thus passing to the nucleus of each daughter cell the exact chromatin complex of the parent cell. Accordingly, in typical mitosis, just after each chromosome has split in the anaphase stage, there is a temporary doubling of the diploid number of chromosomes in a cell. This number is quickly reduced to the typical diploid number as the cytoplasm of the cell splits into two daughter cells and each nucleus receives its diploid quota. Now what appears to be the reverse of the chromatin behavior in normal mitosis is evident in the nucleus of a primary spermatocyte during the reduction division (meiosis), for, here, the chromosomes, instead of splitting, fuse together in pairs—the process of *synapsis*—and the chromosome number in the nucleus of the primary spermatocyte is thus reduced one-half to form the haploid number, though the total amount of chromatin in the nucleus is, of course, unchanged.

But now, as the cytoplasm of the primary spermatocyte prepares to divide to form the two daughter secondary spermatocytes, the temporarily paired chromosomes separate and move in opposite directions, the final result being that the nucleus of each of the secondary spermatocytes receives one chromosome from each pair. Thus the latter have the reduced, or haploid, number of chromosomes. But again it is not the chromosome number in itself that is important; it is the fact that each secondary spermatocyte, as a result of the reduction division, has one complete set of chomosomes and genes—one chromosome of every kind—whereas the somatic cells have two of every kind. (Fig. 187.)

Next comes the division of the secondary spermatocytes to form the spermatids. This appears as a normal mitotic division in which each of the haploid chromosomes splits longitudinally to form two daughter chromosomes, the latter being distributed so as to give one of the halves to each of the spermatids. Their chromatin heritage is transferred unchanged, since each spermatid is gradually transformed into a motile sperm. The essence of spermatogenesis is clear; each sperm nucleus contains not only the reduced or haploid number of chromosomes but one complete set of chromosomes with not a gene missing. When the sperm fertilizes an egg, which also contains a complete haploid set of chromosomes, the diploid number of chromo-

somes—two complete sets, one of maternal and one of paternal origin —will be restored in the zygote nucleus to be maintained in all the cells of the new individual until the time when germ cells are once more formed and synapsis occurs.

Oögenesis

It has been indicated that the maturation of both sperm and egg presents a uniformity in the essential feature, namely, the formation of germ cells bearing a haploid set of chromosomes. In accomplishing this primary aim, the female germ cells pass through a series of maturation stages which conform very closely to those just described in spermatogenesis. There are, however, certain noteworthy variations in oögenesis which should be indicated. The general behavior of the female germ cells as they migrate into the body of the ovary, the formation of the Graafian follicles, and the final release of the female germinal cells to the oviduct have been described in earlier sections (page 319). In the mammalian ovary, the multiplication period, marked by the formation of considerable numbers of primordial germ cells through successive mitoses, occurs before birth, and a considerable number of the resulting oögonia have by that time penetrated into the ovarian tissue where each has become established in a Graafian follicle. The next stage in maturation, the primary oöcyte, is attained by the growth of single oögonia as was seen in the development of the primary spermatocyte. Synapsis, marked by the pairing of the homologous chromosomes, is the basic feature of the primary oöcyte. (Fig. 187.)

Typically, the primary oöcyte stage is the final one occurring in the ovary, and the immature germ cell, released by the rupture of the large Graafian follicle, passes into the oviduct. The completion of the maturation process depends upon union with the sperm cell. If sperm are present in the oviduct, the entrance of the sperm head into the cytoplasm of the primary oöcyte is the signal for the completion of maturation so that fertilization may take place. If no sperm are encountered, the final stages of maturation do not occur and the degeneration of the primary oöcyte soon follows. (Fig. 186.)

The sperm nucleus is temporarily inactive following its entrance, but the primary oöcyte nucleus at once begins the final maturation phenomena. The homologous chromosomes, joined in synapsis, now separate, thus forming two independent haploid sets. One of these passes to each of the daughter cells as the primary oöcyte divides into daughter cells. But the two cells formed from the primary oöcyte are decidedly unequal in size; they consist of a large cell, which is the functional secondary oöcyte, and a miniature cell, the first polar body,

which lies in close contact with the oöcyte like a wart on an apple. Each receives a haploid set of chromosomes. Now comes the final stage in maturation; the chromosomes of the secondary oöcyte divide longitudinally as in normal mitosis to form two haploid sets, one set of which is transferred to the nucleus of the mature egg, while the other goes to the second polar body; for the division of the cytoplasm of the secondary oöcyte, like that of the primary oöcyte, is also very unequal. Practically all the cytoplasm passes to the egg, with only a tiny portion forming the second polar body. Usually the first polar body also undergoes division at this time, so that the final result is the formation

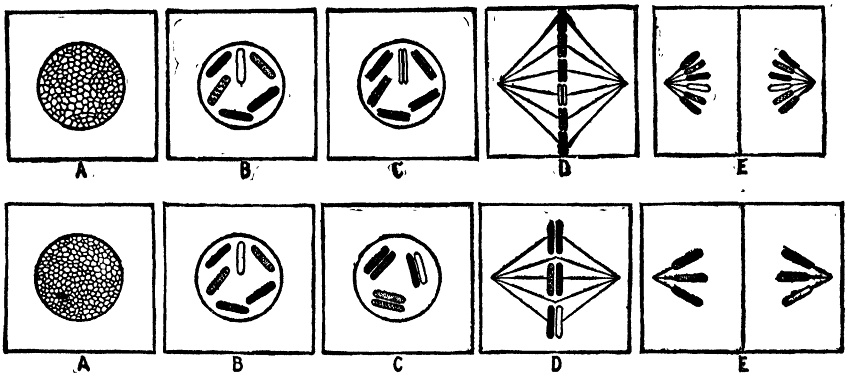


FIG. 188.—Diagrammatic drawings comparing *mitosis* in the somatic cells (above) with *meiosis* during the formation of gametes (below). In mitosis there is a temporary doubling of the diploid chromosome number (*C*, *D*) so that each of the daughter cells (*E*) receives the full diploid number. In meiosis the homologous chromosomes pair (*C*) and then separate (*D*) to give the daughter cells (*E*) the reduced or haploid number. This haploid condition will be maintained through two more divisions to produce four mature sperm in the male, or one mature egg and three polar bodies in the female; all with the haploid chromosome complex. (*Sinnott and Dunn, after Sharp. Modified.*)

of one large functional egg and three nonfunctional polar bodies from each primary oöcyte. The sperm nucleus, which entered the cytoplasm of the primary oöcyte, was transferred to the secondary oöcyte and then to the mature egg. Accordingly, with the completion of maturation and the establishment of the haploid condition in the egg, the gametic nuclei (sperm nucleus and egg nucleus) are ready for the formation of a fusion nucleus, the synkaryon, which determines the heredity of the new individual and the nature of the gene complex which it will transmit to the next generation by way of the gametes. (Fig. 188.)

FERTILIZATION

It will now be profitable to describe the activities that occur in the egg immediately following the completion of maturation. Micro-

scopic observations show that the two gametic nuclei present in the cytoplasm gradually move toward each other until they meet, usually near the center of the egg, with the nuclear membranes in contact for a time. Synchronously the centrosome, which was brought into the egg cytoplasm by the middle piece of the sperm, divides, just as in normal mitosis, and the daughter centrosomes separate to the accompaniment of ray and spindle fiber formation. The nuclear membranes of the two gametic nuclei disappear, and the amazing climax of sexual reproduction and biparental inheritance is at hand: the mingling of the nuclear elements of the two sexes in the synkaryon of the zygote, the process of fertilization. The structural elements of the spindle for the first mitotic division of the new individual is now well established

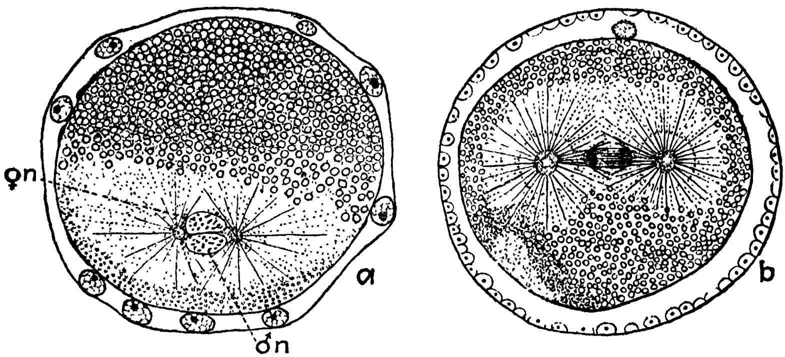


FIG. 189.—Fertilization of an egg (*Ascidian*) showing (*a*) the fusion (amphimixis) of the egg nucleus (♀*n*) with the sperm nucleus (♂*n*) and the inauguration of the first cleavage spindle; (*b*) a later stage showing the cleavage spindle fully developed. (*Seifriz, after Conklin.*)

in the typical prophase stage. This is quickly followed by the metaphase with the paternal and maternal chromosomes meeting for the first time in the equatorial plate and establishing the diploid nuclear complex. Then comes the anaphase stage, with each chromosome splitting longitudinally and moving to the opposite poles of the spindle; finally, the telophase, marked by the division of the cytoplasm to form two diploid daughter cells. And thus a new individual of a new generation, be it frog, chick, or man, is started on its way. Growth, cell division; growth, cell division, with differentiation appearing between groups of cells; primary germ layers, tissues, organs, organ system; and, finally, the mature individual is at hand capable of producing germ cells for the perpetuation of the species through still another generation. Such is the story of sexual reproduction based on biparental inheritance. (Fig. 189.)

Fertilization is often confused with reproduction. From the previous discussion, it is evident that fertilization is really the reverse of reproduction, for reproduction is a process by which cells produce additional cells. In fertilization, on the contrary, there is a fusion of two cells to form a single composite cell, the zygote. It may also be thought that, even though fertilization is not really reproduction, it is essential to this function in the multicellular organism. But, as shown previously, many organisms normally reproduce asexually. In addition, the eggs of a highly developed animal, such as the honeybee, may develop either with or without fertilization. Finally, the experimental results, as previously indicated, have shown that even in some vertebrates it is possible to get the egg to develop without fertilization (page 286). Under normal conditions, then, fertilization may be regarded as having two functions: first, as an activator which is responsible for the inauguration of cell division in the zygote and, second, as a bearer of the parental chromatin which makes biparental inheritance possible. This latter function, namely, conferring biparental inheritance on the offspring, can occur only through fertilization.

With the sequence of events in spermatogenesis and oögenesis in mind, more detailed attention may be given to the basic feature of germ cell maturation, namely, the pairing of the chromosomes in synapsis. It is already apparent that the union of the chromosomes in pairs is not a hit-or-miss arrangement. In the diploid nucleus, as we have seen, are two chromosomes of every kind, one of each pair of the homologous chromosomes being received at fertilization from the male parent and one from the female (page 346). Synaptic pairing occurs only between homologous chromosomes, and so it gives the opportunity for the maternal and paternal genes of the previous generation, having passed through all the stages of the new individual from zygote to adult, to determine the gene complex of the germ cells and through them the inheritance of the next generation. In a word, synapsis preserves the essential continuity between generations and, at the same time, offers opportunity for variation depending upon the nature of the genes from the two lines that pair at synapsis. (Fig. 186.)

Taking, as an example, the chromatin condition in Drosophila with the diploid number of chromosomes established as eight, it may be helpful to portray the maturation changes graphically. Since there are two of every kind of chromosome in the diploid condition, we may designate the four different chromosomes as *A*, *B*, *C*, and *D*. The diploid condition will then be represented by a doubling of each kind of chromosome, or *A*,*A*, *B*,*B*, *C*,*C*, *D*,*D*, to give a total of eight chromo-

somes. This diploid condition is present in all the cells of the organism except the germ cells which have attained the stage of development when synapsis occurs, as in the primary spermatocyte or oöcyte. This process, as shown above, is characterized by pairing of the homologous chromosomes and a reduction in the total number to one-half. This condition may be represented as *AA*, *BB*, *CC*, *DD*. The homologous chromosomes then separate, and one complete haploid set of four chromosomes, *A*,*B*,*C*,*D*, goes to each secondary spermatocyte and, finally, after each has divided, to the mature sperm. The chromosome behavior in human sperm development can be illustrated in the same way by utilizing 24 letters to indicate the 24 different types of chromosome present in the nuclei of the cells.

Sexual reproduction with biparental inheritance makes possible wide variation in the gene complex of the chromosomes united in the zygote nucleus and, therefore, in the heredity of the individuals developing therefrom. No two individuals of the human species or any other species are exactly alike. In order to gain some conception of the possibilities for variation during normal germ cell formation and fertilization, we shall continue our examination of the basic process of synapsis involving the pairing of homologous chromosomes in the germ cells of Drosophila with eight chromosomes in the diploid condition or, as they pair in synapsis, *AA*, *BB*, *CC*, *DD*. Close study of these synaptic pairs shows that each of the homologous chromosomes in synapsis is split longitudinally, just as previously noted in normal mitosis, so that really four chromosome elements, or chromatids, are in close association, thus forming the so-called *tetrad condition.* Viewing a synaptic pair of chromosomes endwise it is possible to see the ends of the four chromatids in close contact. Thus the arrangement of the four synaptic pairs in Drosophila may be graphically shown as

AA BB CC DD
AA' BB' CC' DD'

Tetrad formation may be thought of as a precocious longitudinal splitting of the chromosomes paired in synapsis. In this way, four haploid sets of chromosomes *A*,*B*,*C*,*D* are formed for later distribution to the spermatids and egg cells; one haploid set goes to each spermatid in the male; in the female, one haploid set goes to the functional egg cell and one set to each of the three polar bodies. The important fact to realize is that, though each of the four chromosomes *A*,*A*,*A*,*A* coming from the tetrad condition in synapsis carries the genes for the same characters with exactly the same linear arrangement, variation may occur in the way in which the characters are expressed. To take an example of eye color which, let us say, is determined by a gene or

genes in the synaptic chomosome pair $\frac{AA}{AA}$, the two chromosomes AA of maternal origin might carry genes for blue color, while the other two AA chromosomes of paternal origin carry genes for brown eye color. If this were the case, then two (50 per cent) of the mature sperm would carry genes for blue eyes, and two (50 per cent) would carry genes for brown eyes. But this problem in heredity must be deferred for consideration in the next chapter.

CHAPTER XIV

THE BIOLOGY OF INHERITANCE

In the two preceding chapters, an endeavor has been made to present the essential facts of reproduction, first, as observed from a rather distant reviewing stand from which only the larger features of the process could be observed and, second, as observed near at hand, with the aid of the high-power microscope, in an endeavor to bring to light the basic cellular activities underlying the process of cellular reproduction, whether concerned with the splitting of a single cell into two daughter cells by typical mitosis or the production of a highly differentiated multicellular organism through the union of specialized male and female germ cells.

It has been emphasized that in the reproduction of cells or of multicellular organisms, the new living units must be true to the parental type. At the same time, the processes of reproduction must permit the introduction of limited and controlled variation from the parental cell types. It is evident that, if all the cells formed by the repeated divisions of the zygote remained absolutely true to type, no possibility would exist for the development of the many differentiated types of cells, tissues, and organs as seen, for example, in the vertebrate organism; for all of these cells trace their origin back to one cell, the zygote. We are well aware that a certain amount of easily recognizable variation exists between adult individuals, even when closely related. Body size, color of eyes, color and character of hair, facial features, even the tone of the voice, all have distinctive individual qualities, though conforming to the general pattern to which all the individuals of the group or species belong.

And so the mechanism of heredity, contained in the chromatin material of the nucleus, must be responsible for conformity to type and also for individual variation. Finally, the biologist of today sees no possibility of accounting for the origin of the enormous variety of plant and animal species now present in the world of life except through the hereditary mechanism. Since the establishment of sexual reproduction, it must have been true, just as it is now, that the characters of an offspring are determined by the gene content of the paternal and maternal chromatin received at the time of fertilization. The appear-

ance of a new type or species, past or present, must, therefore, be the result of some alteration in the chromatin-gene complex of a cell or cells in the direct line of descent. The chromatin pattern having once been altered is transferred to the successive generations of daughter cells.

Probably no area in the entire field of biology has aroused more interest and, accordingly, been the object of greater speculation in times past than the field of heredity. As a matter of fact, it has been only in the very recent years that the knowledge of the heredity phenomena has been sufficient to remove them from the realm of speculation and wonder to the field of established fact. At the present time, the essential functional features of the hereditary mechanism are known, though many obscure facts are yet to be brought to light.

THE PARTICULATE NATURE OF INHERITANCE

Present-day knowledge of heredity rests upon the discovery near the middle of the last century that the many characters of an organism are inherited independently of each other and not as a composite group. Thus eye color, to take a common example, is determined independently of the other features that are associated in the complete organism. Credit for this discovery of the particulate nature of inheritance goes to Mendel, an Austrian monk, who became interested in the inheritance of certain characters in peas and used the monastery gardens for his genetics laboratory. Unfortunately his results, published in 1865 in a scientific periodical with limited distribution, lay unnoticed by the scientists of Mendel's time, and it was not until the beginning of the present century, almost forty years after their publication, that Mendel's results were brought to the attention of the biological world. A remarkable thing about Mendel's work is that, without any knowledge of the complex mitotic phenomena associated with inheritance, he was able to deduce the essential facts from his breeding experiments and to establish his laws of heredity that stand essentially unchanged though greatly extended. Biparental inheritance, through the fusion of the male and female gametic nuclei, was not established until 1879, almost fifteen years after the publication of Mendel's results, and the behavior of the chromosomes in the transmission of hereditary characters was not fully brought to light until 1910. In the past quarter of a century, the data accumulated by cytologists and geneticists the world over, culminating in the recent discovery of the giant chromosomes and the analysis of their basic structure, have added tremendously to our knowledge of inheritance and has confirmed and strengthened Mendel's original conclusions.

Let us now take as a working hypothesis the conclusion reached by Mendel that a particular character of an organism may be inherited independently of other characters. Mendel found this to be the case in garden peas, and a wide variety of breeding experiments since then, with many species of plants and animals, have shown that the principle has universal application. We cannot do better at this point than to analyze some of Mendel's results. In the first place, he was very fortunate in the choice of his experimental material, for the species of

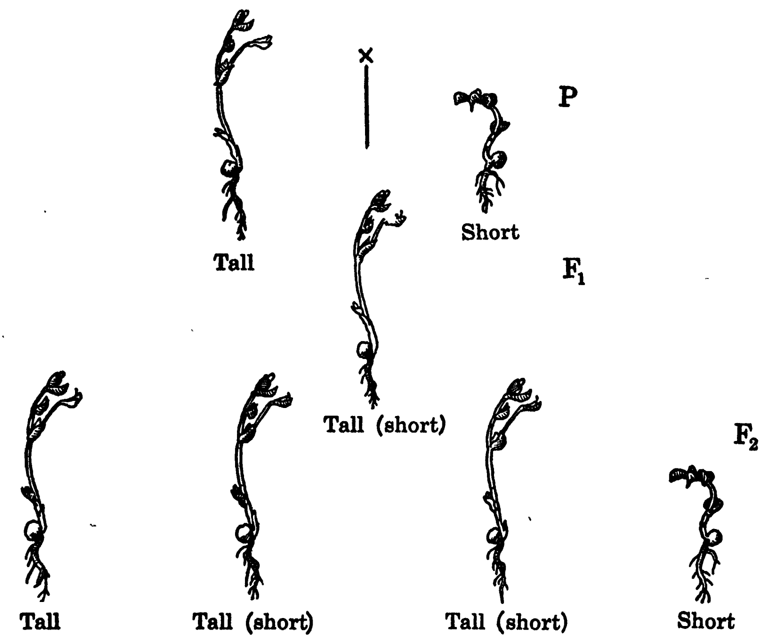


FIG. 190.—Illustrating the inheritance from crosses between a tall and dwarf variety of peas as described on page 359. P, parental generation; F_1, first filial generation: hybrid, tall peas: F_2, second filial generation, produced from F_1 individuals (self-fertilized), show the expected 3:1 ratio between tall and short plants. Note that the two center plants are hybrids like the F_1. (*Woodruff, slightly modified.*)

garden peas that he used presented several interbreeding varieties with a number of clearly recognizable differences, seven altogether, in various structural features. Thus, some of the plants were tall, growing to a height of 6 or 7 ft., while others were short, or dwarf, and never attained a height of more than 1½ ft. Again, some of the plants produced yellow seeds; in others, the seeds were always green. Finally, to take just one more example of the contrasting characters, the seeds were round in some plants and always wrinkled in others. Tall or short, yellow or green, round or wrinkled, here were three very distinct pairs of alternative characters which could be easily observed

and the results from the breeding experiments recorded. Mendel observed that these pairs of characters were truly alternative in nature; that is, the offspring from his crosses were not mixtures but were either tall or short, yellow or green, round or wrinkled. This could mean only that the determiners for these characters did not mingle from generation to generation but remained as distinct entities which could be segregated indefinitely. (Fig. 190.)

In breeding experiments with peas or flies or wheat or horses or any other type of organism, it is essential, for a correct interpretation of the results, that the breeder know the condition of the breeding stock with reference to the particular character or characters in question. Thus it will be found in a general population that, when certain individuals are bred together, all of the offspring will be of one type; for example, all the pea plants produced by one cross will be tall. Contrariwise, the mating of other individuals will produce offspring of two types with reference to a particular character; for example, some will be tall and some will be short. Individuals that breed true with respect to the characters in question are said to be *pure*, or *homozygous;* those which do not breed true are termed *hybrid*, or *heterozygous*.

The terms *homozygous* and *heterozygous* are very important, for they indicate the condition of the chromatin in the germ cells, which, in turn, is responsible for the characteristics of the offspring. Thus, an individual that is homozygous can produce only one type of gamete. A heterozygous individual, on the other hand, will produce more than one type of gamete. If it is heterozygous with respect to only one pair of alternative characters, it will produce two types of gametes and exactly 50 per cent of each type. As an example let us take the pair of alternative characters Tall and Short. An individual plant, heterozygous for this character, will produce 50 per cent of the gametes carrying the determiner or gene for the character Tall and 50 per cent carrying the gene for Short. The organism heterozygous for two pairs of alternative characters, as in the case of Tall and Short, Yellow and Green, will produce four types of gamete and exactly 25 per cent of each type as indicated:

25% carrying genes for Tall and Yellow
25% carrying genes for Tall and Green
25% carrying genes for Short and Yellow
25% carrying genes for Short and Green

As a final example, we may consider the organism heterozygous for three pairs of alternative characters, adding the characters Round and Wrinkled to the two pairs used in the previous example. The organ-

ism heterozygous with respect to three pairs of alternative characters will produce eight types of gamete in equal numbers, that is, 12½ per cent of each type as indicated:

12½% carrying genes for Tall, Yellow, Round
12½% carrying genes for Tall, Yellow, Wrinkled
12½% carrying genes for Tall, Green, Round
12½% carrying genes for Tall, Green, Wrinkled
12½% carrying genes for Short, Yellow, Round
12½% carrying genes for Short, Yellow, Wrinkled
12½% carrying genes for Short, Green, Round
12½% carrying genes for Short, Green, Wrinkled

From the foregoing examination of the gametes produced by the heterozygous individuals, it is clear that the different types of gamete are always produced in equal numbers, and, second, when two or more pairs of alternative characters are present, all possible combinations of the genes between the different pairs occur: Tall can be in combination with Yellow or Green, or with Round or Wrinkled, but Tall can never be in the same gamete with Short; the genes for alternative characters (allelomorphs) are always segregated in separate gametes as indicated a few paragraphs previously. The forming of all possible combinations between the genes for the alternative characters with two or more pairs present was recognized by Mendel under the descriptive phrase *independent assortment* which together with the principle of *segregation* are commonly known as the *Mendelian laws.* The number of possible combinations and, therefore, the number of types of sperm or egg produced can be determined for any number of pairs of alternative characters by 2^n where n equals the pairs of alternative characters involved. Thus, as above, with n equal to 3, there are 2^3, or eight types; with n equal to 5, there are 2^5, or 32 types. And, finally, to take the case in man, if each of the 24 pairs of homologous chromosomes carried a pair of alternative characters, n would equal 24, and the total types of gamete produced would be equal to 2^{24}, or more than 16½ million.

Since, then, as just shown, homozygous individuals produce only one type of gamete, and heterozygous individuals produce two or more types of gametes, depending upon the number of alternative characters carried, it is clear why the former breed true when they are bred together, while the hybrids interbred produce a variety of offspring. But now another interesting and important development comes to light, which Mendel also observed, and that is the principle of *dominance.* This may be illustrated by saying that it is not always possible to determine whether an organism is homozygous or heterozygous by

its appearance. This is due to the fact that one member of a pair of alternative characters is usually dominant over the other, or recessive, member. Thus, in the alternative characters Tall and Short, it is found that Tall is the dominant character, and, as such, dominates the characters of the body (soma) to the exclusion of the recessive character Short. Therefore two types of Tall individuals can be found; the Tall-Tall type, which is homozygous producing only Tall gametes, and the Tall-Short type, which is heterozygous and will produce 50 per cent Tall gametes and 50 per cent Short gametes. It is obvious that only one type of the recessive short individual occurs, namely, the Short-Short homozygous type, for the Short-Tall heterozygous individuals are all tall; the character Tall is always dominant over Short. The breeder who wishes to establish a pure line with respect to a certain character or characters must find out the dominant-recessive relationship and then make the appropriate matings. It must always be remembered, as noted previously, that possibly the most important discovery of Mendel was that the complete heritage of an organism was not assembled in a single unit but consisted of a great number of independent unit characters (particulate inheritance) each of which was separately transmitted to the offspring in conformity with the general principles of independent assortment and segregation. (Fig. 190.)

With an understanding of particulate inheritance, hybridization in its relationship to gamete formation, segregation, independent assortment, and dominance, the basis of Mendelian inheritance is well established, and the results obtained from the crosses are easy to understand. The starting point in determining the characters to be expected in the offspring from the mating of any two individuals is always: What genes do the gametes of the two parents carry with respect to the characters in question? The simplest possible case would occur in the mating of two homozygous individuals which, as we know, can produce only one type of gamete. For a change, let us take the inheritance of certain characters in guinea pigs, which are familiar to every one and which have been widely used in breeding experiments as well as in a wide variety of other types of biological experiment. The inheritance of certain visible characters in the hair, such as color, length, and smoothness, is convenient to use. We shall consider, first, the inheritance of color. The colored, or Black, condition, which we can for convenience designate by the letter C, is dominant over the White, or albino, condition which we may designate by the small c since this condition is recessive. The small c, then, represents a lack of color, or pigment, and gives white hair. Just as noted above in the

case of the peas, there will be two types of black animals in a general population that cannot be distinguished by their appearance: the pure, or homozygous, individuals that carry only dominant genes Colored-Colored, for convenience represented as *CC*, and produce only one type of gamete, namely *C*; and the hybrid, or heterozygous, individuals that carry both the dominant gene *C* and the recessive gene *c* for the alternative character, that is, Colored-White or more conveniently represented as *Cc*. The *Cc* individuals, of course, produce gametes of two kinds: 50 per cent *C* and 50 per cent *c*. (Fig. 190.)

The mating of a pure male (*CC*) with a pure female (*CC*) can produce only colored offspring (*CC*) like the parents because no other types of gamete are produced by either of the parents. The mating and the results of breeding two homozygous individuals can be indicated graphically thus:

(I) Sperm $C \times$ egg C = zygote CC

The same results are obtained when a recessive white male (*cc*) is mated with a recessive white female (*cc*) for they can produce only one type of gamete (*c*) and the results of all such matings will be:

(II) Sperm $c \times$ egg c = zygote cc

Another possible type of mating of homozygous individuals is that in which a homozygous dominant (*CC*) is mated with a homozygous recessive (*cc*). The result of such a cross is the production in every case of hybrid or heterozygous colored individuals (*Cc*) thus:

(III) Sperm $C \times$ egg c = zygote Cc

The reciprocal mating with a recessive white male (*cc*) and a homozygous colored female (*CC*) will give the same results, thus:

(IV) Sperm $c \times$ egg C = zygote Cc

With these easily understood results from homozygous matings in mind, let us next consider the results of mating a hybrid-colored male guinea pig (*Cc*) with the same type of female (*Cc*) as in the preceding paragraph. Both produce two types of gamete in equal numbers, that is, 50 per cent sperm *C*, 50 per cent sperm *c* by the males; and 50 per cent eggs *C*, 50 per cent eggs *c* by the females. Obviously, as shown above in the case of peas with two pairs of alternative characters, the possible combinations of sperm and eggs are as follows:

(V)
Sperm $C \times$ egg C = zygote CC
Sperm $C \times$ egg c = zygote Cc
Sperm $c \times$ egg C = zygote cC
Sperm $c \times$ egg c = zygote cc

It has been found convenient in determining the possible combinations of the gametes to use a square in which are separate spaces for the zygotes, with the various types of sperm arranged along the left side, and the eggs along the top, as follows:

(VI)

Sperm \ Eggs	*C*	*c*
C	*CC*	*Cc*
c	*cC*	*cc*

An analysis of the foregoing results shows that three different types of zygote are possible from the mating of the two hybrids with

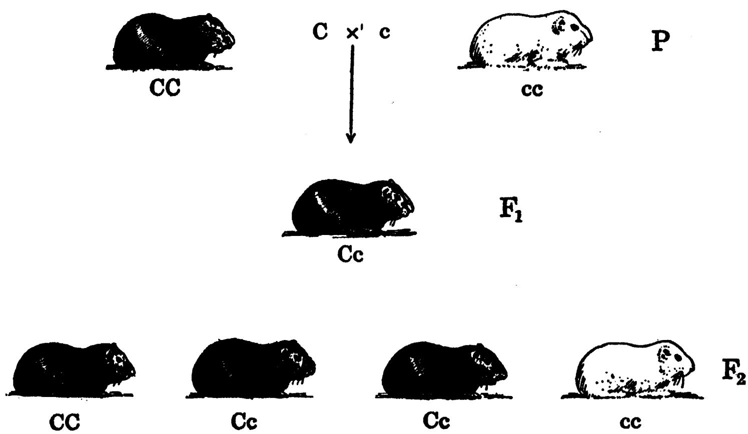


FIG. 191.—Illustrating the inheritance of hair color when homozygous black guinea pigs (*CC*) are mated with albino guinea pigs bearing no pigment (*cc*), as described on page 361. (*Woodruff, slightly modified.*)

respect to one pair of alternative characters, namely, pure black (*CC*), hybrid black (*Cc* and *cC*; the result is the same whether a particular gene is carried by the sperm or egg), and pure white (*cc*). Accordingly, since both the pure dominant (*CC*) and the hybrid dominant (*Cc*) have the same appearance—in this case, they are black—the offspring of this hybrid mating are expected in the ratio of 3 black animals to 1 white animal or 75 per cent black to 25 per cent white. (Fig. 191.)

As a matter of fact, this expected 3:1 ratio does not always appear, because the union of the gametes at fertilization is at random; that is, it is always a matter of chance as to whether a particular egg will be fertilized by a *C* sperm or by a *c* sperm, just as it is always a matter of chance as to whether heads or tails will come up when a coin is pitched.

There is always a chance that heads may appear successively; but if the process is continued for a large number of times, say 1,000, the likelihood is that heads-tails ratio will be pretty close to 50 per cent heads to 50 per cent tails. In the same way, if the numbers of offspring obtained from hybrid matings are large, the chances are very good that the ratio of black animals to white animals will be very close to the Mendelian ratio of 75 per cent black to 25 per cent white. Thus Mendel reported from the offspring of monohybrid individuals, differing with respect to one pair of alternative characters, that the ratio obtained in a total of 1,064 offspring was 73.9 per cent showing the dominant character to 26.1 per cent showing the recessive character. Many other breeding experiments with a wide variety of plants and animals have given comparable results.

Referring again to the results of the hybrid matings as given above, it is clear that on the basis of their appearance the animals can be placed in two groups: black and white in a 3:1 ratio. From the standpoint of their germinal constitution, however, three groups, namely, *CC*, *Cc*, and *cc*, are present in a 1:2:1 ratio, or 25 per cent homozygous dominant (*CC*) to 50 per cent hybrid dominant (*Cc*) to 25 per cent homozygous recessive (*cc*). It will be well to introduce the terms *phenotype* and *genotype* at this point. The phenotype of an organism has reference to the appearance of the organism without regard to the germinal conditions; the term genotype refers to the actual germinal constitution. We may say, then, in the above matings that the expected phenotype ratio is 3 animals showing the dominant character black to 1 animal showing the recessive character white, whereas the expected genotype ratio is 1 (25 per cent) homozygous dominant (*CC*) to 2 (50 per cent) heterozygous dominants (*Cc*) to 1 (25 per cent) pure recessive (*cc*). From the standpoint of heredity, it is obvious that the phenotypes can be discarded; it is only the actual germinal constitution, or genotype, that counts in the formation of gametes which, in turn, are responsible for the transmission of characters to the next generation. (VI.)

The three genotypes *CC*, *Cc*, *cc* of the monohybrid matings present various possibilities for the succeeding generations. It is clear that the pure dominants (*CC*) and the recessives (*cc*) will continue to produce the same types if mated with individuals of the same genotype, that is, *CC* with *CC* and *cc* with *cc*. The hybrids (*Cc*) will continue to produce offspring in the 1:2:1 ratio if mated with hybrid animals (*Cc*) as shown in table (VI). Another possibility lies in the mating of the *CC* animals with *cc* animals which, as shown in (IV) above, gives, in all cases, the hybrid condition (*Cc*). The final possibility lies in the

mating of homozygous animals with heterozygous. Thus the pure blacks (CC) can be mated with the hybrid blacks (Cc), or the white animals (cc) can be mated with the hybrid condition (Cc). In either of these crosses it will be found that the expected ratio of the offspring is: 50 per cent bearing the genotype of one parent and 50 per cent bearing the genotype of the other parent. Thus

(VII) $CC \times Cc$

Sperm \ Eggs	C	c
C	CC	Cc

(VIII) $cc \times Cc$

Sperm \ Eggs	C	c
c	cC	cc

Considering the homozygous-hybrid matings (VII), it is seen that there is only one phenotype—all the offspring are black—and two genotypes, CC and Cc, corresponding to the two parental types with an expected 1:1 ratio. In the second example (VIII), the two phenotypes, black and white, occur and also two genotypes, Cc and cc, corresponding to the two parental types and with an expected 1:1 ratio. Recalling for a moment the results of mating two hybrids as shown in square (VI) above, it will be seen that the results of homozygous-hybrid matings, as in (VII) and (VIII), can be read in the two horizontal columns of (VI). In the upper horizontal column we have the results shown as in (VII); the lower column reads the same as (VIII) of the homozygous-hybrid matings. The vertical columns of the square (VI) give the same results with the sexes reversed.

The description of the various matings makes it evident that Mendelian inheritance depends primarily upon the number of types of gamete produced by the parents, and this in turn, as shown, is directly dependent upon the number of pairs of genes for alternative characters present. When an organism is homozygous, as in the genotype CC or in the genotype cc, the gene for an alternative character is not present, and all the gametes must be of one kind. The hybrid, or heterozygous, condition, on the contrary, bears genes for one or more pairs of alternative characters as shown above in the Tall-Short hybrids in the peas and the Colored-White (Cc) hybrids that we have been considering in the guinea pigs. The addition of other pairs of alternative characters increases the number of gametes produced according to the ratio 2^n where n represents the number of pairs of alternative

characters or the degree of hybridization (page 369). This may be indicated by the terms *monohybrid* where one pair of alternative characters is present, *dihybrid* where two pairs of alternative characters are considered, and *trihybrid* where there are three pairs of alternative characters. Our study of Mendelian inheritance, so far, has been concerned with the monohybrid condition represented by one pair of alternative characters Colored-White, or *Cc*, and giving two types of gamete *C* and *c* and four possible combinations. Now the results obtained from matings of dihybrids or trihybrids or polyhybrids with even greater hybridization conform exactly to the results obtained in the monohybrid matings; they only present more types of gamete and correspondingly more possible combinations between gametes, as will be shown in the following paragraphs.

In the dihybrid condition with its two pairs of alternative characters will be 2^2, or four types of gamete. To see the possibilities inherent in this condition we may take another visible hair character in the guinea pig, namely, length of hair, which has been shown to be a Mendelian character with the alternative pair of characters Short-Long. The short-haired condition is dominant and may be designated as *S*, and the long-haired condition which we shall represent by *s* is recessive. The dihybrid animals, then, with two pairs of alternative characters differing with respect to color of hair (*Cc*) and length of hair (*Ss*) are indicated in the genotype constitution *CcSs*. The four types of gamete produced by these dihybrids are *CS* (genes for black and short), *Cs* (genes for black and long), *cS* (genes for white and short), and *cs* (genes for white and long). Mating two dihybrids, then, gives four types of sperm and four types of egg and the possibility of 16 combinations when the gametes unite in random fertilization to form the zygote. Again the square shows all the possibilities (IX).

(IX)

Eggs / Sperm	*CS*	*Cs*	*cS*	*cs*
CS	*CCSS* (1)	*CCSs* (2)	*CcSS* (3)	*CcSs* (4)
Cs	*CCSs* (2)	*CCss* (7)	*CcSs* (4)	*Ccss* (5)
cS	*CcSS* (3)	*CcSs* (4)	*ccSS* (8)	*ccSs* (6)
cs	*CcSs* (4)	*Ccss* (5)	*ccSs* (6)	*ccss* (9)

An analysis of the various possibilities in the dihybrid square shows that, out of the 16 possible combinations, there are four phenotypes corresponding to the four types of gametes, the appearance of which may be described as follows: black, short-haired animals; black, long-haired animals; white, short-haired animals; and white, long-haired animals; or, stated in another way, those which show both dominant characters, those which show one of the two dominant characters, those which show the other dominant character, and those

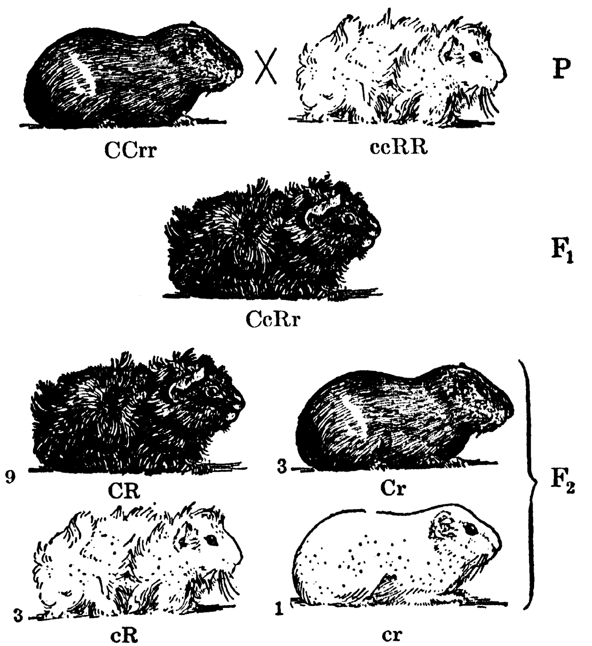


FIG. 192.—Illustrating the inheritance of hair color and another alternative character (rough or smooth), giving a dihybrid condition. Note that one of the parents (*CrCr*) is dominant for color (*C*) and recessive for smoothness (*r*); whereas the other parent (*cRcR*) is recessive for color (*c*) and has the dominant character (*R*) which produces a rough coat. All of the F_1 dihybrids show the two dominant characters. (*Woodruff, slightly modified.*)

which show neither of the dominant characters. These occur in different proportions; the first group with both dominant characters is the largest with 9 out of the 16 animals, or 56.25 per cent. They are shown in the zygotes numbered (1), (2), (3), and (4). Three out of the 16, or 18.75 per cent, express the dominant character Black. They are shown in zygotes numbered (5) and (7). Three out of the 16, or 18.75 per cent, show the other dominant character Short. They are shown in zygotes numbered (6) and (8). One individual out of 16, or 6.25 per cent, may be expected to show neither dominant character,

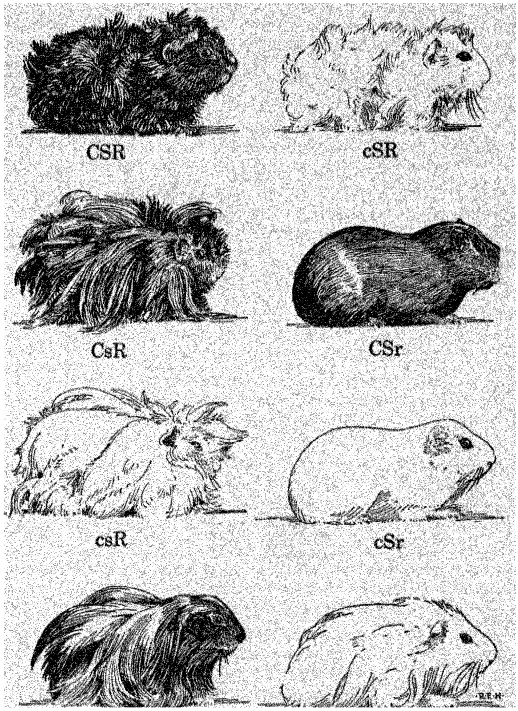
as indicated in number (9). Thus we have the dihybrid phenotype ratio of 9:3:3:1. (IX.)

The 16 possible dihybrid combinations give 9 different genotypes which, as just seen, are numbered from 1 to 9. Among the genotypes is one pure dominant (1) which has received the two dominant genes *CS* from both parents and, of course, can form only *CS* gametes; also one pure recessive (9) which received the two recessive genes *cs* from both parents. In addition to (1) and (9) there are two other genotypes (7) and (8) which are also homozygous, having received the same genes from both parents. Four of the genotypes (4) are dihybrids like the parents, the genes received, from either the sperm or egg, giving the genotype *CScs*. Eight of the genotypes are monohybrids (2), (3), (5), (6) with two each of four different combinations. It will be helpful to examine one of these to see just why they are monohybrids. Let us take the genotype condition as shown in (2), namely, *CS* from one parent and *Cs* from the other. If now the genes for color and the genes for length are arranged in pairs, we have *CCSs*. It is thus seen that such an animal is homozygous with respect to hair color; that is, it can produce only one type of gamete for this character, namely, gametes bearing the gene *C*. It can produce two types of gametes, *S* and *s*, with respect to length of hair. In brief, then, this is a monohybrid and will form 50 per cent gametes with *CS* genes and 50 per cent with *Cs* genes.

In summarizing the expected results from the dihybrid matings with respect to hybridization, it is thus found that four (25 per cent) are homozygous, 8 (50 per cent) are monohybrids, and four (25 per cent) are dihybrids like the parents. Once again emphasis should be laid on the fact that the various ratios just considered are not absolute, since fertilization is always at random, and, therefore, no prediction can be made as to which one of the four types of sperm will fertilize a particular egg, as explained above in the consideration of the monohybrid ratios. Finally, it should be noted that the results from the matings of dihybrids with homozygous individuals and also with monohybrids are shown in the various horizontal columns of the dihybrid square (IX) as observed previously in the monohybrid square (VI). Thus, for example, the zygotes expected from the matings of a dihybrid with a homozygous dominant are shown in the top horizontal column.

The principles operating in the monohybrid and dihybrid matings, which have been considered in some detail, are unaltered in the trihybrids with three pairs of alternative characters or in any polyhybrid with still more pairs of alternative characters. Since this is the

case, it is not necessary for the geneticist to consider, in general, matings in which account has to be taken of more than one, two, or three alternative characters. In nature, however, with thousands of heritable characters present in the organism it would be impossible to find an individual homozygous for all the genes involved or even individuals with only one, two, or three pairs of alternative characters; they are all polyhybrids.



CSR cSR

CsR CSr

csR cSr

Csr csr

FIG. 193.—The possible F_2 phenotypes from a trihybrid cross between one parent carrying the three dominant characters for pigmentation, short hair and rough coat (upper left-hand corner) and the other parent a pure recessive with no color, smooth coat and long hair (lower right-hand corner), as described on page 368. (*Woodruff, slightly modified.*)

Brief consideration of the trihybrid condition will be sufficient to show the increased possibilities associated with the addition of a third pair of alternative characters. Continuing with our study of the inheritance of visible hair characteristics in the guinea pig, it has been found that a curly or rough condition of the hair coat is alternative to a straight or smooth condition. The condition Rough, or R, is dominant over Smooth, or r. The homozygous dominant for colored, short, rough hair thus has the genotype $CSRCSR$, producing only CSR

gametes, and the recessive has the genotype *csrcsr*, producing only *csr* gametes. Matings of the pure dominant and the pure recessive invariably give offspring in the next generation (F_1) showing colored, short, rough hair like the dominant parent and with genotype *CSRcsr*. This trihybrid condition with three pairs of alternative characters, that is, with *n* equal to 3, forms 2^3, or 8 types of gamete and 12½ per cent of each type. Making all the possible combinations in an independent assortment, the eight types of gametes are found to be: *CSR*, *CSr*, *CsR*, *Csr*, *cSR*, *cSr*, *csR*, and *csr*. The construction of the trihybrid square as in the previous cases, but for eight types of gametes, shows that 64 possible combinations are represented in the zygotes of the F_2 generation. The eight phenotypes, corresponding to the gametes, may be expected to appear in the ratio of 27:9:9:9:3:3:3:1 in a total of 64 animals, but, as we understand, since fertilization as always is at random, the chance of getting exactly this particular ratio in any group of 64 animals is very slight. It will be found that there are 27 genotypes of which 8 are homozygous and 19 are heterozygous. Out of a total of 64 animals in the F_2 generation, the expectancy is that 8 (12.5 per cent) will be homozygous; 8 (12.5 per cent) will be trihybrids like the parents; 24 (37.5 per cent) will be dihybrids; and 24 (37.5 per cent) will be monohybrids. (Figs. 193, 194.)

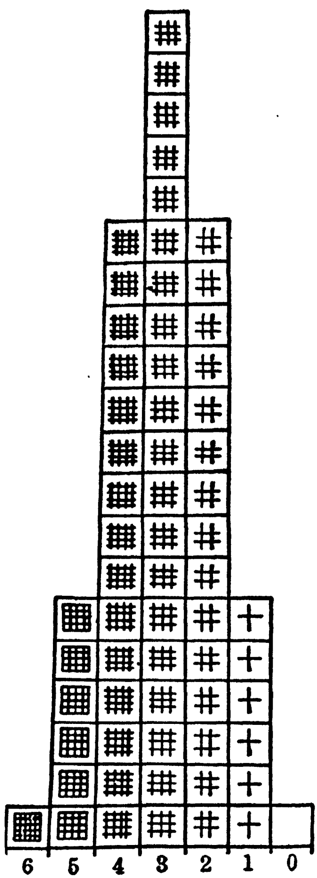


FIG. 194.—Diagram illustrating the expected distribution of the 64 possibilities in the F_2 generation of a trihybrid. (*Walter.*)

To summarize the ratios in the various hybrids the table at the top of page 369 may be helpful.

Blending Inheritance.—From the descriptions just given of the various hybrids, it is evident that the dominance of a particular character in the phenotype is a striking feature of Mendelian inheritance, but it must be stated at once that dominance is not a universal feature, for there are numerous instances in which the genes for alternative characters are of equal value in the determination of the characters in the phenotype just as they always are in the gene-complex of the

(X)

	Types of gamete	Types of phenotype	Types of genotype	Possible combinations
Homozygous (CC)	1	1	1	1
Monohybrid (Cc)	2	2	3	4
Dihybrid ($CcSs$)	4	4	9	16
Trihybrid ($CcSsRr$)	8	8	27	64
Polyhybrids (n pairs of alternative characters)	2^n	2^n	3^n	4^n

gametes. This condition is commonly referred to as *blending inheritance* because the hybrid offspring show a mixture, or blend, of a particular character; dominance is lacking. One of the most common examples of this is seen in the common snapdragon in which plants

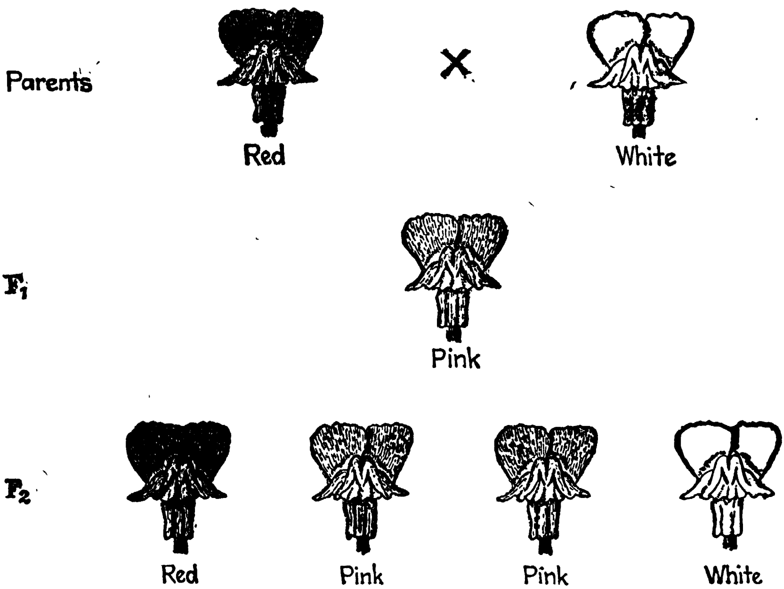


FIG. 195.—Illustrating blending inheritance in the snapdragon when homozygous red and white individuals are crossed as described on page 369. (*Sinnott and Dunn.*)

are found with red, white, or pink blossoms. The breeding experiments show that, when a pure red plant is crossed with one bearing white blossoms, all of the hybrid offspring will have pink flowers. The pink flowers may be regarded as intermediate in color between the red and white of the two parental plants. It is apparent from these

results that neither red nor white are dominant in the phenotype. If now the hybrid F_1 plants bearing pink flowers are crossed, three types of colored offspring will appear in the F_2 generation in a 1:2:1 ratio or 25 per cent red:50 per cent pink:25 per cent white. This is the ratio expected from the mating of monohybrids as shown in square (VI). If we let *C* represent the gene for red color and *c* the gene for white color, then the pure reds have the genotype *CC* and the whites the genotype *cc*. The F_1 hybrid pink offspring will contain both genes, that is, *Cc*, and will produce gametes *C* and *c*. Crossing of these monohybrids gives the 1:2:1 ratio as shown in table (XI) and also in Fig. 195.

(XI)

Sperm \ Eggs	*C*	*c*
C	*CC* (red)	*Cc* (pink)
c	*Cc* (pink)	*cc* (white)

Thus when dominance is lacking, the genotype is revealed by the appearance of the phenotype. Many other examples of blending inheritance are known, as for example, in the inheritance of size in rabbits where the offspring of matings between large and small races are intermediate in size. The latter when interbred show a segregation of size in the next generation. Earlier, it was thought that the results obtained from some of these examples with incomplete dominance did not conform to the Mendelian laws, but further study has shown in practically every case that they fall into line. From our standpoint, the important thing to note is that segregation of the genes in the gametes of the hybrids with dominance lacking occurs just as in other hybrids where complete dominance is found.

Lack of dominance may be expressed in other ways than by the so-called blending inheritance, as just shown in flower colors. Thus, in the matings of red cattle with white, the F_1 offspring show a characteristic roan color. If the individual hairs of the hybrid roans are examined, it will be found that they are equally divided between red hairs and white hairs so that both of the alternative genes are expressed in the color pattern of the roan animals. The hybrid roan-colored animals, when interbred, produce offspring as in monohybrid matings, namely, 25 per cent red to 50 per cent roan to 25 per cent white, just as do the snapdragons. Another well-known example of the same type of inheritance is in the Blue Andalusian fowls, which never breed

true but produce offspring with three types of color in the ratio of 1:2:1 as follows: 25 per cent white to 50 per cent blue to 25 per cent

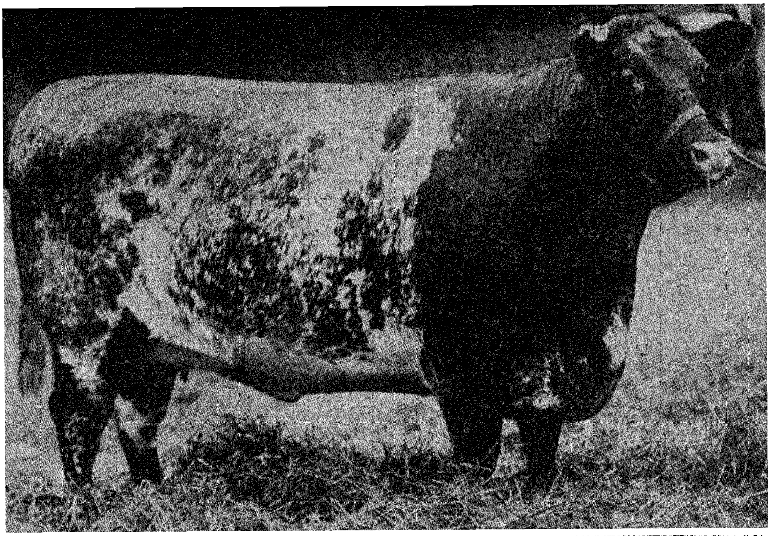


FIG. 196.—Photograph of a roan, short-horned cow. This color condition occurs in animals heterozygous for red and white hair color, as described on page 370. (*Shull, after McPhee and Wright.*)

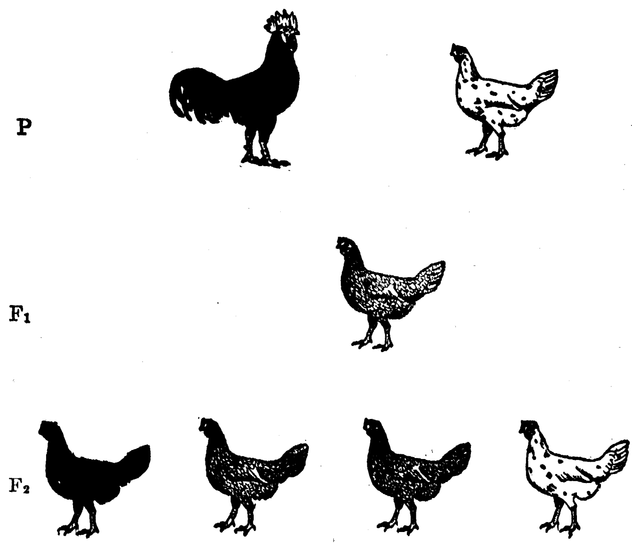


FIG. 197—Illustrating the inheritance of blue in Andalusian fowls; a condition shown only by the hybrid. (*Sinnott and Dunn, modified.*)

black. It is apparent that the so-called Blue Andalusian type is a monohybrid with respect to color, bearing genes for black and for

white. Accordingly, the blue color is produced in all the offspring from the matings of the homozygous blacks and whites. (Figs. 196, 197.)

Multiple Factors

The cases of dominance that have been described thus far have been ones in which a single pair of genes was operating, but it is well established that, in many instances, several pairs of genes are concerned in the development of a particular character, the condition known as *multiple genes* (multiple factors). This puzzling condition was first noted in the results obtained from breeding certain grains, such as oats and wheat. When, for example, a variety of brown-seeded oats was crossed with a white-seeded variety, both being homozygous, all of the plants in the next generation had brown seeds that were distinctly lighter in color than the brown-seeded parent. When these hybrid F_1 plants were interbred, it would normally be expected, as we know, that a phenotype ratio of 3 brown to 1 white would appear in the offspring. But not so in this case. The dominant brown color appeared in the ratio of 15 dominant brown-colored seeds to 1 recessive white seed, or 93.75 per cent to 6.25 per cent. An examination of the brown seeds showed considerable variation in the depth of color. It was then seen that this condition was just what would be expected if two factors or genes were associated with this color character, thus giving the dihybrid condition for color, with four different types of gamete and 16 possible combinations (page 364). Representing the two factors for brown color as C_1C_2 and the recessive alternative genes for white as c_1c_2, the genotype of the pure dominant would be $C_1C_1C_2C_2$ with all gametes C_1C_2; that of the pure recessive $c_1c_1c_2c_2$, with all gametes c_1c_2. All the dihybrid offspring would then have the genotype $C_1c_1C_2c_2$ and would produce four types of gamete as shown in the dihybrid square, which conforms to that shown in (IX) above.

(XII)

Eggs / Sperm	C_1C_2	C_1c_2	c_1C_2	c_1c_2
C_1C_2	$C_1C_1C_2C_2$ (1)	$C_1C_1C_2c_2$ (2)	$C_1c_1C_2C_2$ (3)	$C_1c_1C_2c_2$ (4)
C_1c_2	$C_1C_1C_2c_2$ (2)	$C_1C_1c_2c_2$ (7)	$C_1c_1C_2c_2$ (4)	$C_1c_1c_2c_2$ (5)
c_1C_2	$C_1c_1C_2C_2$ (3)	$C_1c_1C_2c_2$ (4)	$c_1c_1C_2C_2$ (8)	$c_1c_1C_2c_2$ (6)
c_1c_2	$C_1c_1C_2c_2$ (4)	$C_1c_1c_2c_2$ (5)	$c_1c_1C_2c_2$ (6)	$c_1c_1c_2c_2$ (9)

When the results of the matings are analyzed, it becomes apparent that the brown color of the seed increases in intensity in correspondence with the number of genes for color present. Thus individuals with the genotype $C_1C_1C_2C_2$ form seeds with the greatest amount of brown pigment, with a decrease indicated in the genotypes with fewer of the color-bearing genes C_1 and C_2 as in the series $C_1C_1C_2c_2$, $C_1c_1C_2c_2$, $C_1c_1c_2c_2$, and with no brown pigment whatever in the pure recessive $c_1c_1c_2c_2$. (Fig. 198.)

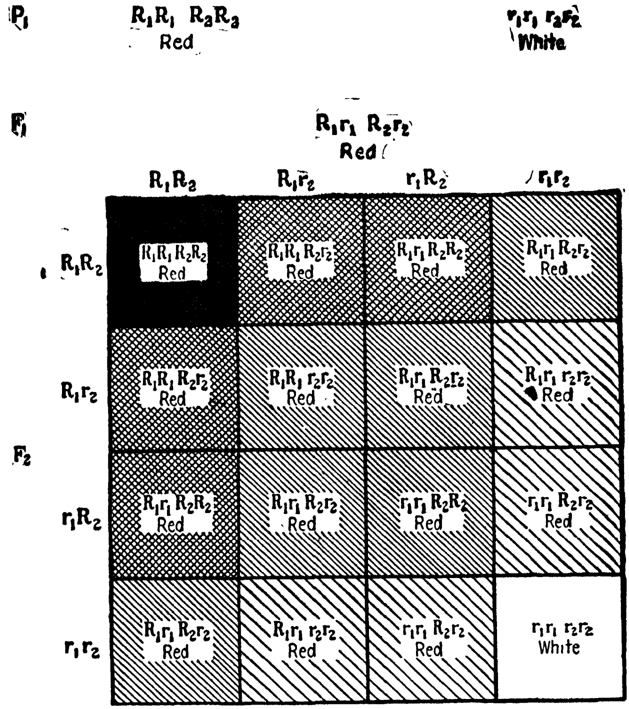


FIG. 198.—Illustrating results of crossing two varieties of wheat, one with two factors for red seeds ($R_1R_1R_2R_2$) and the other with the factors for white seeds ($r_1r_2r_1r_2$). This multiple-factor condition is described on page 372. (*Sinnott and Dunn.*)

In the matings of certain varieties of red-seeded and white-seeded wheat, it was found that a trihybrid condition for color, with three pairs of genes, was present so that, in the F_2 generation, the ratio of colored seeds to pure white was 63 colored out of 64. In other words, on the average one pure recessive appeared out of 64 possible combinations, which is the condition in a trihybrid cross. Hair color in animals has been shown, in some instances, to be due to multiple factors, and it is also evident that skin color in man is another example. Thus, in man, there are two or three pairs of genes for color, with the intensity

of the color in the skin of the hybrid, or mulatto, offspring of white and negro parents being governed by the number of dominant genes present, as just seen in oat seeds. If we take the colored conditions as being dihybrid with the color genes C_1C_2, then the genotype of the pure negro with black skin can be given as $C_1C_1C_2C_2$ and the recessive white as $c_1c_1c_2c_2$, just as in the case of the dihybrid color factor shown in (XII) above and in Fig. 198.

The discovery of multiple genes, that is, the knowledge that more than one pair of genes were concerned with the production of a particular character, brought a great many cases of inheritance into the Mendelian fold that did not, at first, appear to conform to the established principles. At the same time, increased emphasis came to be laid upon the fact that the characters exhibited in the organism, in most cases at least, were not the result of one pair of genes acting during development but of many genes. In the determination of eye color in Drosophila, for example, it is known that more than 20 pairs of genes are operating, and essentially the same situation exists with regard to the determination of wing characters. Furthermore, the various genes for eye and wing characters are not even located in the same pair of homologous chromosomes. In the determination of sex, however, it is clear that the gene mechanism is localized in one pair of chromosomes, though various genes may be at work. But aside from the determination of sex, no evidence exists that all the genes for a particular character or associated with the development of a certain organ are located in a particular chromosome. Thus to refer again to the eye of Drosophila, the numerous genes concerned with color and various other characteristics have been found to be located in all four of the synaptic pairs. Furthermore, the genes in a particular chromosome, though maintaining a rigid linear relationship as shown by the synaptic phenomena, appear to be promiscuously arranged with respect to the characters that they determine, so that, for example, a gene for eye color may be situated close to a gene responsible for the development of some character in the body or wings. Since, however, comparatively few of the total number of genes have been located, it may be that the apparent irregularities do not give a true picture.

But possibly the most important result coming from an understanding of multiple factors was the light thrown upon the problem of selection. Practically all types of domesticated varieties of plant and animal, which man has found valuable for his multitudinous needs, have been subjected to selection since the earliest times; certain individuals being chosen in each generation for the production of the next generation. Such selection has been made in order to strengthen and

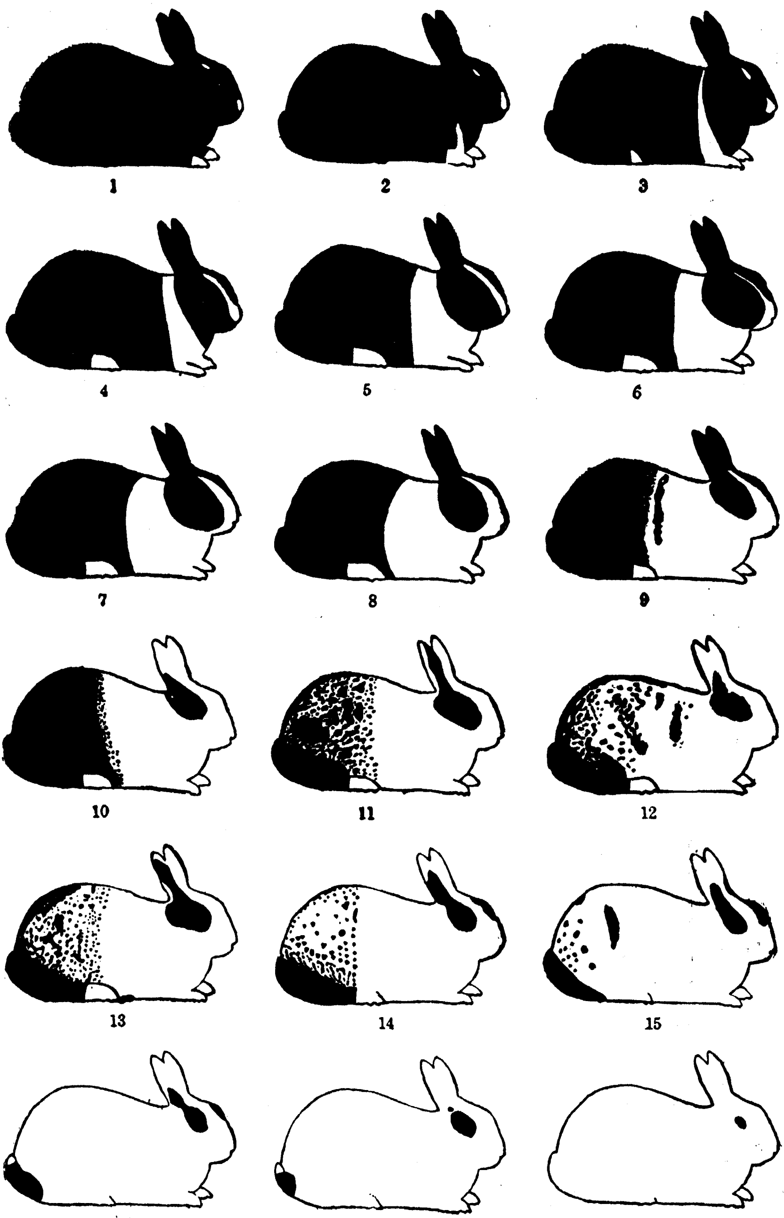


FIG. 199.—Illustrating variations in hair color in Dutch rabbits. By systematic selection the average pigmentation "of a race of Dutch rabbits may be gradually but permanently changed either in a plus or in a minus direction." The extreme of pigmentation is shown in 1, and the opposite condition in 18. (*Castle, "Genetics and Eugenics," Harvard University Press.*)

establish a certain desirable attribute which was particularly well displayed in the organisms selected for breeding; more milk in cows, more speed in race horses, more power in draft horses, more returns per acre in the grains due to higher productivity, to greater ability to resist disease, or to earlier ripening qualities; the examples are almost unlimited. (Fig. 199.)

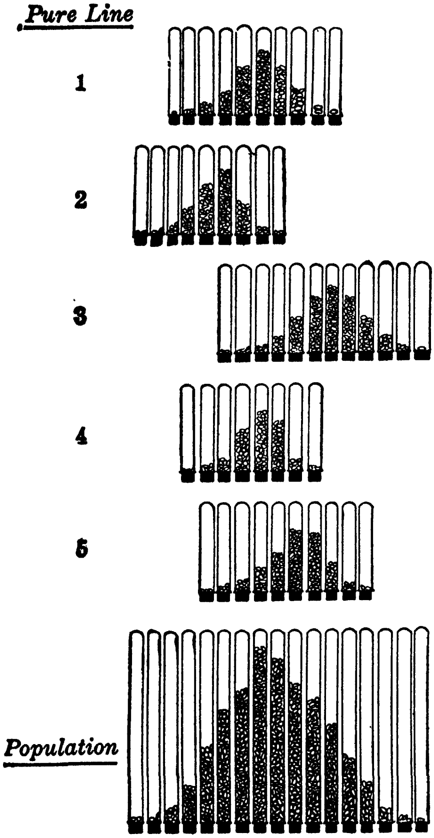


FIG. 200.—Diagrams illustrating variation in weight of pure lines of beans (1–5). The test tubes containing beans of the same weight are arranged vertically. The general population formed by combining the pure lines is shown below. (*Walter, after Johannsen.*)

Now the fact is, of course, as almost everyone knows, that selection as practiced by practical breeders, who knew nothing of the Mendelian principles or genes, has been successful and is responsible for most of the improvement that has been made in our present-day varieties of domesticated plants and animals over the undomesticated types. But it is now clear that the improvement of types by selection is based upon the gradual accumulation, generation by generation, of the genes responsible for the production of the desired character for which selection is being made. In other words, where selection is effective, several pairs of genes, multiple genes, are associated with the development of the character in question so that the selection, for example, of certain animals for breeding, which show the optimum expression of a desired character, means the accumulation of more genes for this character and a correspondingly greater expression of it in the next generation. Selection, then, to be effective must occur in a mixed population, or, in Mendelian terms, the individuals must be heterozygous. In a pure line, where all the individuals are homozygous, selection can have no effect, for all the genes governing the character in question are then present in the genotypes of the homozygous indi-

viduals. Thus, to take a very simple example, selection would have no effect in increasing the color in the brown-seeded oats with the genotype $C_1C_1C_2C_2$, for all the genes for color are present, or in decreasing the color in plants with the genotype $c_1c_1c_2c_2$. (Figs. 198 to 200.)

LINKAGE

If the preceding descriptions of the Mendelian phenomena have been followed carefully, it is probably already apparent to the reader that the segregation of the genes in gamete formation and their recombination in the zygote nucleus at the time of fertilization exactly parallel the behavior of the chromosomes as described in the closing pages of the previous chapter. Of course, this must be true if it is kept in mind that the chromosomes are really strings of genes arranged in linear fashion, like beads on a necklace. Thus the same terminology might be used with a pair of homologous chromosomes as with genes in the case of a pair of alternative characters, such as Colored (*C*) and White (*c*). In the parent hybrid individual with the diploid condition *Cc*, both chromosomes *C* and *c* would be present in all the cells, but when the gametes are formed following synapsis and reduction, each gamete with the haploid condition will receive only one chromosome, that is, either *C* or *c*, just as each gamete contains either the gene *C* or the gene *c*. Fertilization, following mating with an organism carrying the same chromosomes, will restore the diploid condition and give the opportunity for a sperm with the *C* chromosome to combine either with an egg with the *C* chromosome or with an egg bearing the *c* chromosome, thus giving zygotes with the three genotypes as given above (VI) in the monohybrid matings. This can be carried further with additional homologous pairs of chromosomes for the Short and Long (*Ss*) as in the dihybrid, and the Rough and Smooth (*Rr*) as in the trihybrid. The point is clear; a particular gene is always in a particular chromosome and cannot act independently of that association.

This condition leads at once to the question of the association, or linkage, of the genes present in a particular chromosome. It was early recognized in breeding experiments that certain characters always appeared together in an individual; both were present or both were absent, but never one without the other. The explanation was long lacking, but it is now known that the linking of certain characters in an individual is due to the fact that the genes for these characters happen to lie in the same chromosome and must accompany this chromosome wherever it goes. Since the number of characters and the

corresponding genes in the highly developed organism runs into the thousands and there are only a relatively few chromosomes in which all these genes lie, it becomes apparent that many genes are situated, or linked, in a particular chromosome and must always go along with it. It was stated in the previous chapter that some 2,500 genes were arranged in linear fashion in one chromosome of Drosophila (page 336). All these genes must, therefore, go into one gamete with that chromosome and give rise to a corresponding group of associated characters in the offspring. The genes in a particular chromosome constitute a *linkage group*. The total number of linkage groups in an organism, as determined by a study of linked characters in breeding experiments, must, then, correspond to the haploid number of chromosomes as seen under the microscope. This has been found to be the case in two important instances where data are available. In Drosophila, as we know, four different chromosomes are to be observed when the haploid nuclei are observed under the microscope. The breeding experiments with Drosophila likewise show four linkage groups. It has been found in Indian corn that the 10 haploid chromosomes found by the cytologist check with breeding experiments of the geneticist showing 10 linkage groups. (Fig. 179.)

Linkage necessarily restricts the independent assortment of genes in gamete formation. Independent assortment can occur only in cases where the pairs of alternative characters that are being considered lie in different chromosomes or linkage groups. To take a specific example in the dihybrid *CScs*, which we studied in (VI) above, if the two pairs of alternative genes are present in the same pair of homologous chromosomes, only two types of gamete, *CS* and *cs*, can be formed. This will be understood if it is remembered that the homologous chromosomes separate after having been temporarily fused in synapsis, and then each divides to form a total of four chromosomes which are distributed to the spermatids of the male or to the egg and the three polar bodies of the female. In this case, then, the chromosome bearing the genes *CS* unites with its synaptic mate bearing the genes *cs*. Following this temporary union, they separate and are segregated in the secondary spermatocytes or, in the female, in the secondary oöcyte and the first polar body. In this case, one of the secondary spermatocytes would carry the *CS* chromosome, and the other would receive the *cs* chromosome. In the final stage, each chromosome divides longitudinally so that two *CS* chromosomes and two *cs* chromosomes are distributed to the four spermatids or, in the female, to the egg and three polar bodies. Thus, as stated above, when two genes are present in the same chromosome, there is no possibility

of independent assortment, and only two types of gamete are formed in a 1:1 ratio, as in the case of the monohybrid.

Though it had long been observed that certain characters were associated in the organism, the first evidence obtained by the laboratory geneticist that supplied an explanation of the phenomenon was in connection with the so-called *sex-linked* characters. A sex-linked character is one in which the gene is carried on the sex chromosome (X chromosome) which determines the sex of the zygote at the time of fertilization, as stated previously (page 339). Before discussing the behavior of sex-linked characters, it may be well to reexamine the inheritance of sex in the light of our added knowledge of inheritance phenomena. It will be recalled that the female produces only one type of gamete with respect to sex; all eggs contain an X chromosome. Thus the female is homozygous in this respect. The male, on the other hand, is heterozygous for sex and produces two types of sperm: the X sperm and the Y sperm (which is the synaptic mate) in equal numbers as in the normal monohybrid condition. As shown above in matings between homozygous and monohybrid individuals, the expected Mendelian ratio is 1:1, or, in this case, 50 per cent males and 50 per cent females. Since, however, fertilization is always at random, the sex of any particular mating depends on whether the X sperm or the Y sperm reached the egg first. The possibilities of sex inheritance, as just described, may be shown graphically as follows:

(XIII)

Sperm \ Eggs	X
X	XX ♀
Y	XY ♂

Now in the case of sex-linked characters it is established that the X chromosome carries other genes beside those which determine sex. Since these genes actually lie in the X chromosome with those which determine sex, they must be carried along just as in any case of linkage, discussed above. One of the best examples of this is found in the inheritance of red and white eye color in Drosophila. In this case, the gene for red in the X chromosome is dominant over the gene for white, and so, whenever an X chromosome bearing the gene for red is present in the genotype, the animal has red eyes. Accordingly, if a red-eyed male is mated with a white-eyed female, all the sons will have white eyes and all the daughters will have red eyes, as we shall now see. Since the gene for eye color and the gene determining sex are on

the same chromosome, independent assortment of the two genes cannot occur. The red-eyed male acts as a monohybrid and produces equal numbers of two types of gamete; one type bearing X with gene *R* for red which we may indicate as X^R, and the other, gametes bear-

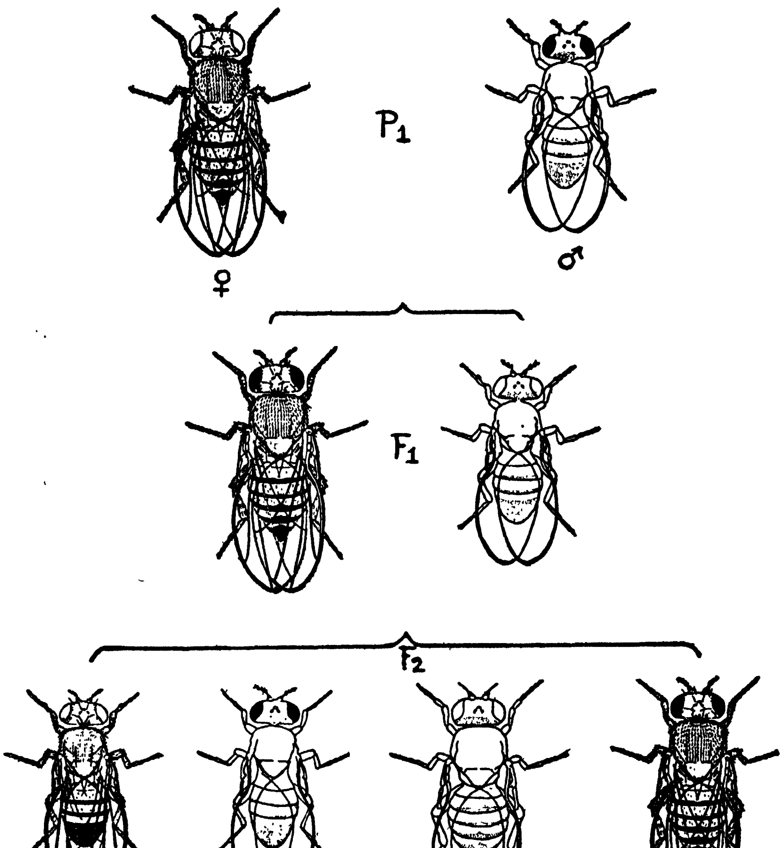


FIG. 201.—Illustrating the possibilities of sex-linked inheritance from crosses between a white-eyed female Drosophila and a red-eyed male. All of the F_1 females are red-eyed (left); all of the males are white-eyed (right). The results of matings between these two genotypes are shown in the F_2 generation and described on page 381. (*Slightly modified from Morgan, "Scientific Basis of Evolution," W. W. Norton & Company, Inc.*)

ing Y. The white-eyed female is homozygous with respect to sex and also eye color and, therefore, produces only one type of gamete, indicated as X^r, all of which contain the gene for the recessive white eye color. This is another case of mating a monohybrid with a homozy-

gous individual (VII), (VIII), (XIII), and the expected results in the F_1 generation, namely, 50 per cent white-eyed males and 50 per cent red-eyed females are illustrated in the following square. (Fig. 201.)

(XIV)

Sperm \ Eggs	X^r
X^R	$X^R X^r$
Y	X^r Y

Let us carry sex-linked inheritance a step further by next mating these males and females of the F_1 generation (XIV). It will be seen that the male, as always, is heterozygous with respect to sex, producing two types of gametes X^r and Y. But neither of these carry the red gene, so the male is homozygous with respect to eye color. The female, as always, is homozygous with respect to sex, producing only one type of gamete, X, but is heterozygous for eye color with two types of gamete, X^R and X^r. The union of these male and female gametes involves a typical monohybrid crossing (VI) with four possible zygotes, as shown in the square.

(XV)

Sperm \ Eggs	X^R	X^r
X^r	$X^r X^R$	$X^r X^r$
Y	X^R Y	X^r Y

It is seen that the offspring show the following possibilities; 25 per cent with the genotype $X^r X^R$ will be red-eyed females; 25 per cent with the genotype $X^r X^r$ will be white-eyed females; 25 per cent with the genotype X^R Y will be red-eyed males; and 25 per cent with the genotype X^r Y will be white-eyed males. All of these possibilities are illustrated in Figure 201. Mating between a white-eyed male, X^r Y, and a red-eyed female homozygous for the red-eyed condition, $X^R X^R$, gives the same results for color inheritance as in any mating of two individuals homozygous for a particular character. Thus all of the hybrid F_1 offspring of both sexes from this cross will show the dominant character, red eye, and these, when interbred, will normally give, in the next generation, 3 red-eyed individuals to 1 white; made up of one homozygous red-eyed female, $X^R X^R$, one hybrid red-eyed female, $X^R X^r$; one red-eyed male, X^R Y, and one white-eyed male, X^r Y. (Fig. 201.)

Color Blindness.—Long before the mechanism of sex-linked characters was understood, it had been noted that a defect in human

vision, known as *color blindness* and characterized by an inability to distinguish between red and green color, was inherited in a peculiar fashion. In the first place, this defect is much more common in men than it is in women, and, secondly, it is transmitted between the two sexes in an unusual way which can be explained on the assumption that the defective gene is carried in the X chromosome. **There is** an added feature, however, not found in the inheritance of eye color in Drosophila which, as we have just seen, behaves as a simple Mendelian dominant; that is, the red eye appears in either sex when the

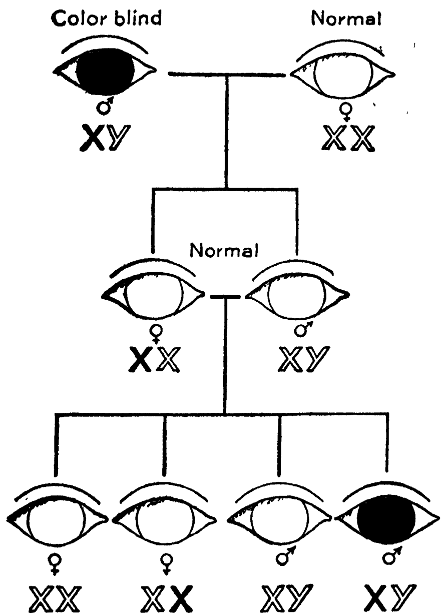


FIG. 202.—Diagram illustrating the inheritance of color blindness from a color-blind father and normal mother as described on page 383. X-chromosomes carrying this defect are shown in solid black. (*Sinnott and Dunn, after Dunn, Courtesy of the University Society.*)

gene is present in the X chromosome. The gene for color blindness, which we may designate as *c*, for some unknown reason acts as a recessive in the female and must, therefore, be present in both of the X chromosomes in order to produce color blindness, as $X^c X^c$. If it is present in only one of the X chromosomes, as $X^c X$, the woman will not have defective color vision, but she will be a carrier for color blindness. These carrier females will form two types of gamete with respect to this character, namely, gametes bearing the normal X and gametes bearing the defective X^c, with the result that the gene for color blindness will be transmitted to the next generation. In the

male, the gene for color blindness acts as a dominant so that the man is always color-blind when the X chromosome carries the defective gene as $X^c Y$.

Various possibilities for the offspring result from matings between normal males, color-blind males, normal females, carrier females, and color-blind females. One common example may be taken to show the inheritance from a color-blind father with the genotype $X^c Y$. Two types of gamete will be produced, namely, X^c and Y. If union occurs with a normal female with the genotype XX and therefore producing only X gametes, the same possibilities exist as in a monohybrid-homozygous combination as already indicated in (VII) and (VIII). As shown below (XVI), all the children of both sexes will have normal vision, but the daughters will be carriers.

(XVI)

Sperm \ Eggs	X
X^c	$X^c X$
Y	X Y

Continuing this analysis one step further to the grandchildren, we consider the possibilities for color blindness inherent in the offspring of normal fathers and carrier mothers (XVI). It will be seen that the male gametes are free from the defective genes and form normal X gametes and Y gametes. The mother, as a carrier with the genotype $X^c X$, produces X^c gametes and X gametes, and the results in the offspring can be shown in the monohybrid square (XVII).

(XVII)

Sperm \ Eggs	X^c	X
X	X X^c	X X
Y	X^c Y	X Y

It is evident that the defective gene of the male grandparent (XVI) under these conditions may be expected to produce color blindness in one-half of the grandsons and carriers in one-half of the granddaughters. All the other grandchildren, both male and female, will be free from the defective gene. Another defective gene associated with the sex chromosome is responsible for hemophilia or bleeding. It behaves in the same way in inheritance. (Fig. 202.)

Lethal Genes.—The typical monohybrid ratio of 3 dominant to 1 recessive, which has been so thoroughly established in various organisms, is supplanted by a 2:1 ratio in the expression of certain characters. The explanation of this ratio was not clear for some time, and

then it was discovered from the proper experimental crosses that one of the expected F_2 genotypes was entirely missing in the offspring from certain monohybrid crosses, and this was due, it became evident, to the presence of a so-called lethal gene which resulted in the death of all individuals when present in a homozygous condition. This lethal condition was first shown in the gene for yellow hair color in mice. It is known that yellow color is dominant, and accordingly it would be expected that the two genotypes YY and Yy would be found among the yellow animals. But yellow animals crossed with black invariably gave a 1:1 ratio instead of all yellow as expected with matings of homozygous dominants (YY) and homozygous recessives (yy). Also when the yellow animals were crossed with yellow, the color ratio in the offspring was always 2 yellow to 1 recessive (black or brown or

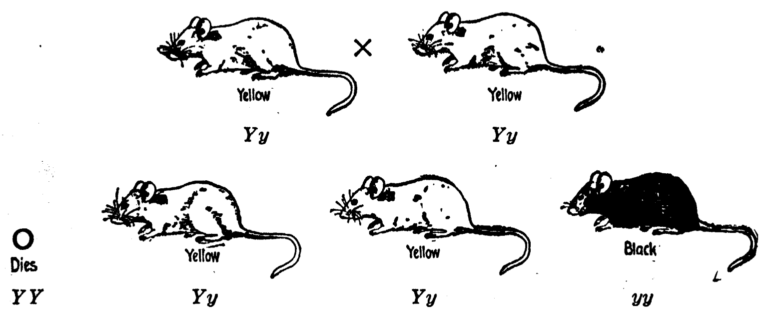


FIG. 203.—Illustrating inheritance of a lethal factor in mice. The homozygous yellow embryos (*YY*) die, as described on page 384. (*Sinnott and Dunn, slightly modified.*)

gray). In a study of over 1,200 mice, the 2:1 ratio was always closely maintained. The breeding results are just what would be expected if all the yellow animals were heterozygous (Yy). It is clear that such is the situation. The homozygous yellow (YY) is lethal, and the zygotes that receive this combination at fertilization die before birth. (Fig. 203.)

Another very interesting example of a lethal gene that has been very thoroughly studied is associated with the so-called *creeper chicken,* which is characterized by a marked reduction in the length of the legs (also the wings) so that the animals appear to be squatting on the ground, and their locomotion is more of a creep than a walk. It has been shown by the proper crosses that the gene for the creeper character always acts as a dominant when present. Normal animals never have creeper offspring, but normals crossed with creepers give a 1:1 ratio, and creepers crossed with creepers give a ratio of 2 creepers to 1 normal, as in the yellow mice. The creeper condition is therefore

heterozygous (*Dd*). The homozygous creeper (*DD*) dies. An examination of the eggs being incubated shows that the homozygous creeper embryos die at about the fourth day of incubation. If account is taken of the dead creeper embryos, then the expected 3:1 ratio from breeding monohybrids is obtained. The square gives the results when creepers, all bearing the genotype *Dd*, are crossed:

(XVIII)

Sperm \ Eggs	*D*	*d*
D	*DD* (dies)	*Dd* (creeper)
d	*Dd* (creeper)	*dd* (normal)

Crossing Over.—The description of Mendelian inheritance given so far shows an amazingly rigid system for the transmission of characters from generation to generation. Thus it has been shown that the genes are arranged in definite linear fashion in the chromosomes and are sorted out or segregated in mechanical fashion during gamete formation in correspondence with the pairs of alternative characters. Furthermore, it has been shown that there are relatively few chromosomes as compared with a large number of genes, and, accordingly, great numbers of genes are linked together in each chromosome. Thus linkage limits the possibility of independent assortment and, thereby, the possible types of gamete produced. The rigidity of the system is somewhat lessened by the fact that fertilization is at random; but with a small number of chromosomes, as in Drosophila with a haploid number of 4, only 16 combinations are possible with other gametes as shown in the dihybrid square (IX). And so a Drosophila sperm from a pure dominant, with four haploid chromosomes, *A*, *B*, *C*, *D*, has the possibility of uniting with an egg from an individual with the same chromosome grouping or with an egg from one of the 15 other chromosome combinations such as *A*, *B*, *C*, *d*; *A*,*B*,*c*,*d*; etc.; and, finally, to *a*, *b*, *c*, *d*, in which all four chromosomes carry the recessive gene. In man, with 24 different types of chromosomes, the possibilities of chromosome combinations are, of course, greatly increased, but even so there appears to be no way to get new heritable characters introduced into the system. The purpose of this section is to introduce certain important features associated with inheritance that markedly decrease the rigidity of inheritance, which has just been summarized, for we now know a number of important phenomena associated with

the hereditary mechanism that introduce new and, to some extent, unpredictable heritable features into the germ plasm that, thereafter, become part and parcel of the hereditary melange for transmission to succeeding generations. (Fig. 204.)

The first of these flexible features is a process associated with synapsis and aptly designated as *crossing over*. The title is descriptive and means that, under certain conditions, genes located in one of the synaptic mates may cross to the other member of the pair during synapsis. That such occurred in certain insects during gamete formation was observed by the cytologist Janssens nearly thirty years ago,

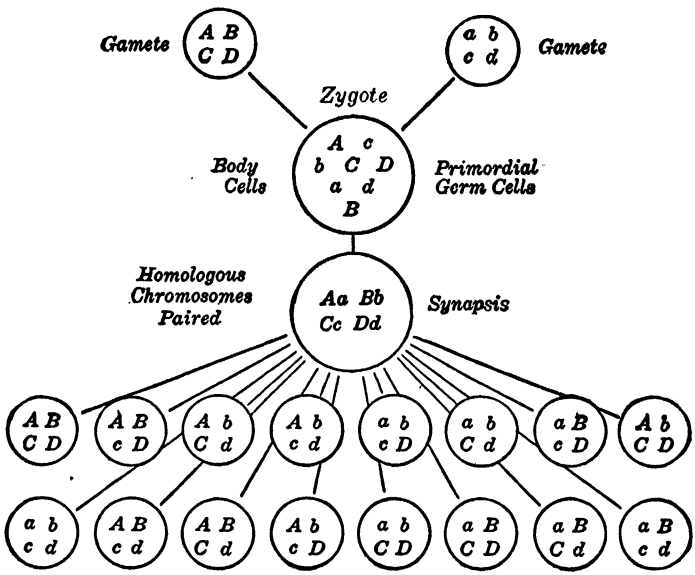


FIG. 204.—Diagram illustrating the 16 possible types of gametes resulting from the union, in the previous generation, of two gametes, each bearing four chromosomes, as described on page 385. (*Woodruff.*)

but it was the more recent results obtained by breeding experiments in fruit flies that confirmed the cytological findings. Crossing over, since it occurs with predictable frequency in the case of certain matings, is to be regarded as a normal feature of synapsis. It produces new possibilities, *recombinations*, for the genes concerned. (Fig. 205.)

The classic example of crossing over, which will serve admirably for our purpose, occurs in Drosophila. Female flies with two dominant linked genes for Gray Body (*G*) and Long Wings (*W*), when mated with the so-called *vestigial* male flies that carry linked recessive genes for the alternative characters Black Body (*g*) and Short Wings (*w*), produce only hybrid gray, long-winged offspring. This is just what would be

expected since the pure gray, long-winged flies with the genes *G* and *W* in the same chromosome can produce only one type of gamete, namely, *GW*; and the recessive black, short-winged animals, under the same conditions, can also produce only one type of gamete, namely, *gw*. Fertilization between these gametes produces 100 per cent hybrid F_1 offspring with the genotype *GWgw*. These individuals, of course,

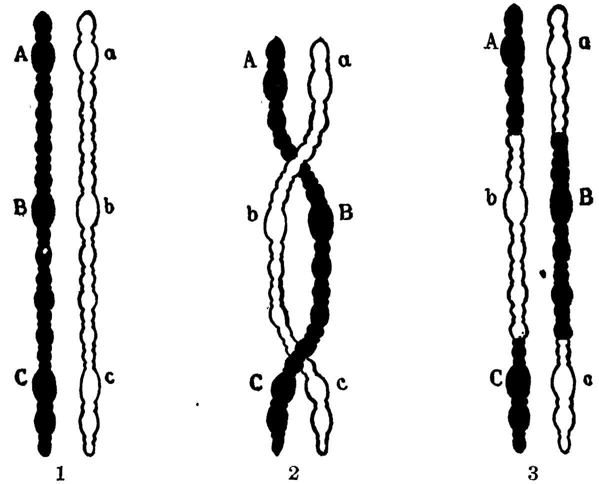


FIG. 205.—Diagram illustrating crossing over between homologous chromosomes during synapsis, giving new arrangements of the genes (recombinations). If no crossing over occurs the chromosomes separate after synapsis carrying the same genes (1). Crossing over at two points (double crossing over) is shown in (2) and the results of the recombinations in (3). (*Sinnott and Dunn, slightly modified.*)

behave as monohybrids and produce two types of gamete in equal numbers: *GW* gametes and *gw* gametes. Now, if the monohybrid females (*GWgw*) are mated with the pure recessive males (*gwgw*), the expected Mendelian ratio is 50 per cent hybrid dominants (*GWgw*) and 50 per cent pure recessives (*gwgw*) as in the typical monohybrid-homozygous mating, as shown in the square.

(XIX)

Sperm \ Eggs	*GW*	*gw*
gw	*GWgw*	*gwgw*

Actually, however, repeated experiments showed that the expected 1:1 ratio did not appear. In all cases, approximately 82 per cent of the animals were divided equally between the hybrid dominants and the

pure recessives, whereas in 18 per cent of the offspring two unexpected varieties appeared in equal numbers, namely, Gray animals with short wings, that is, the genotype *Gwgw*, and black flies bearing long wings, or the genotype *gWgw*. The results were decisive, and, therefore, it was apparent that either something was wrong with the accepted ideas of Mendelian inheritance or else some condition existed that had not been taken into account. The latter proved to be correct. The unknown factor was the phenomenon of crossing over. It is amply confirmed that synapsis results not only in the pairing of the genes for alternative characters but also, in many instances, in the actual transfer, or cross over, of portions of the pairing chromosomes from one to the other so that when the chromosomes separate after synapsis, each actually contains one or more pieces of the other member of the pair. Necessarily the genes in the detached pieces of the chromosomes are also transferred to the other synaptic mate. Thus, in the example above, one of the homologous chromosomes with the linked genes *GW* became *Gw* after synapsis, and, in the other, the linkage *gw* was changed to *gW*. Consequently, as shown in the square, there were four types of gametes for union with the *gw* gametes of the recessive male.

(XX)

Sperm \ Eggs	*GW*	*Gw*	*gW*	*gw*
gw	*GWgw*	*Gwgw*	*gWgw*	*gwgw*
	41%	9%	9%	41%

Sex-linked inheritance gave the clue to linkage; linkage gave the clue to crossing over; crossing over gave the clue to the arrangement of genes in the chromosomes and enabled the investigators in this field to accumulate data for the preparation of chromosome maps through the discovery that the relative frequency, or percentage, of crossing over was in direct relation to the distance between the genes concerned. Genes lying close together have very little chance to shift their position, or cross over, to the other chromosome of the pair; genes lying relatively far apart have a much greater chance. As an example of the methods that have been employed, let us consider the position of the genes for another character in the same chromosomes, in relation to the genes *Gg* and *Ww*. Designating one end of the chromosome as zero, we can arbitrarily locate genes *G* and *W* at two points along the chromosome, but they must be separated by 18 units from each other

in correspondence with the percentage of crossovers as determined by the breeding experiments. The appropriate breeding experiments with the genes for the new character, which we shall indicate as *Nn*, show a percentage crossover in relation to *Gg* of 30, whereas the percentage of crossovers of *Nn* in relation to *Ww* is only 12. Since the percentage of crossovers is higher when the distance between the genes involved is greater, the results from the breeding experiments show that the gene *N* must be located 12 linear units below *W* and 30 points below *G*. This is the only point that will conform to the percentages of crossovers, that is, 18 per cent between *G* and *W*, 12 per cent between *W* and *N*, and 30 per cent between *G* and *N*. Cumulative data from a large number of characters in Drosophila have established the positions of the corresponding genes in certain chromosomes and the development of the so-called *chromosome map*. Chromosome maps have also been established for certain characters in other organisms, notably Indian corn. Particularly gratifying to the biologist is the fact that the positions of the genes shown in the chromosome maps, which were determined on the basis of crossing over, have been shown in many instances to rest on a firm basis by the data derived from the microscopic study of the chromosome complex which will now be indicated. (Figs. 181, 211.)

Mutations

Leaving the phenomenon of crossing over, which has been found to be a normal and predictable feature of Mendelian inheritance, consideration must next be given to a variety of unpredictable and abnormal inheritance patterns that occur as the result of several types of irregularity or aberration in the chromosomal complex. These are commonly grouped under the term *mutation;* the term coming from the Latin verb *mutare*, meaning "to change." Chromosomal aberrations, or mutations, in the germ cells are effectual in producing somatic mutations in the resulting offspring. The latter, in turn, in producing gametes with the mutated chromosomes, continue to pass the mutations along. Once in the germ plasm, the mutation is there to stay unless a later mutation in this same region again alters the chromatin pattern. It is possible for mutations to occur also in the chromatin of one or more of the body cells of an organism. Succeeding generations of cells, directly descended from the mutated cell, will have the same change impressed upon them, but, in this case, the mutation cannot get into the stream of germ plasm for transmission to offspring. However, somatic mutations of this kind are not uncommon in plants

and are known as *bud mutations*. Since plant tissues are usually capable of regeneration, it is possible to remove the mutated tissue and to grow it independently or as a graft on another plant of the same species where it will produce the mutated type of cells and tissues. Bud mutations of this type are responsible for many standard varieties of apples and other fruits.

Mutations have their origin in the various types of chromosomal aberrations. Some of these involve changes in considerable areas of the chromosomes and so come within the range of microscopic vision; marked structural abnormality being visible in one or more of the chromosomes. Suppose, for example, that the offspring produced by the mating of individuals with known genotypes exhibit some unusual character. Microscopic examination of the chromosome complex from both germinal and somatic cells may reveal changes in

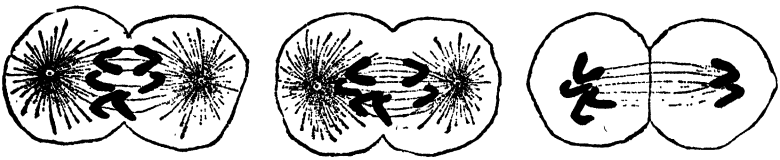


FIG. 206.—Diagrams illustrating nondisjunction in which both members of a pair of homologous chromosomes go to one cell (to the left), thus giving one cell with four chromosomes and one cell with two chromosomes. (*Shull.*)

the normal pattern. Thus it was found some years ago that certain females of Drosophila had unexpected eye color and various other abnormalities. The basis of this altered inheritance was revealed by the microscopic studies that showed that such females had a Y chromosome in addition to the XX, thus giving an XXY instead of either XX of normal females or XY of normal males. This abnormal condition was traced to the fact that the parental females were producing mature eggs carrying XX instead of X. A failure of the X chromosomes to separate (nondisjunction) at the last maturation division caused the production of XX gametes. Instead of a single chromosome being added to the chromatin complex of the gametes, as in the case of the XX condition just described, many instances are known in which an altered heredity pattern is the result of a doubling or tripling or even a larger multiple of the normal chromosome number, the condition of heteroploidy (page 340). In this way, distinct varieties of a particular species are established and continue as a standard type, as seen, for example, in the well-known varieties of wheat with 7, 14, and 21 chromosomes or in certain distinct species of Chrysanthemum with 18, 36, 54, 72, and 90 chromosomes in the diploid

condition. The case of Drosophila with 12 chromosomes instead of 8 has been mentioned previously. (Figs. 184, 206.)

Other chromosomal aberrations that result in altered heredity may involve the breaking, or fragmentation, of a chromosome and the later association of one or more of the detached pieces with a chromosome of another linkage group. Thus chromatin material may be deleted from one member of a pair of homologous chromosomes and attached to a chromosome belonging to another pair. As a result, a certain percentage of the gametes will be deficient for certain genes, but other gametes will have genes added. Deletion, translocation, inversion are all established possibilities of chromatin mutations, many of which involve chromosome alterations of sufficient size to be checked with the microscope. In very recent years, our knowledge of the relations between chromosomal abnormalities and altered somatic structures has been markedly increased by two things; first, the discovery that the X-ray irradiation of germ cells undergoing development would change the normal chromatin setup in the gametes, and second, the discovery of giant chromosomes in the nuclei of the salivary gland cells that were large enough to make visible altered chromatin patterns in areas much too small to be studied in normal-sized chromosomes (page 336). In addition to their extraordinary size, the giant chromosomes are undergoing synapsis, though present in somatic cells, and this synaptic condition is of the highest value in the detection of chromatin irregularities in either of the pairing chromosomes (page 347). For, in synapsis, absolute exactness of gene position throughout the length of the pairing chromosomes is necessary. The genes for all of the alternative characters linked together in a particular pair of chromosomes must be at exactly the same levels

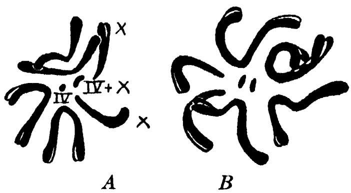


FIG. 207.—Drawings of the diploid chromosomes of the Drosophila female (XX) to illustrate the translocation of chromatin material. In *A* it is noted that there is a normal sized chromosome (IV) and an abnormally large one (IV + X); the increased size of the latter is due to a translocation of a piece from one of the X chromosomes. This translocation was due to the irradiation of germ plasm of one of the parents. In *B* it is noted that the translocation has affected both of the IV chromosomes, and therefore this individual was homozygous for the altered chromatin condition. *Cf.* Fig. 179. (*Painter*, "*Science in Progress*," *Yale University Press.*)

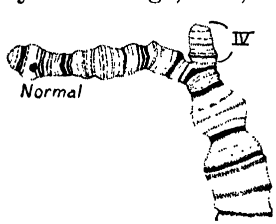


FIG. 208.—Drawing of the terminal portion from one of the giant chromosomes (II), of a salivary gland cell, Drosophila, showing the translocation of a piece of the fourth chromosome (IV). (*Painter*, "*Science in Progress*," *Yale University Press.*)

in the synaptic mates. With size of the genes well below microscopic visibility, this means an exactness of construction with relation to gene position in chromosomes far beyond anything that can be achieved in machine construction. (Figs. 207, 208.)

Since every gene must be in its exact position when synapsis occurs, this process is now recognized as one of the most important tools for

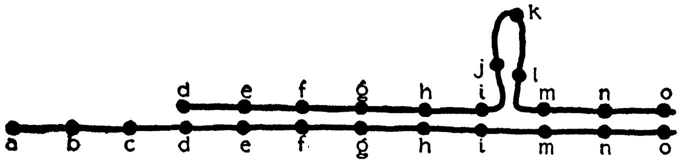


FIG. 209.—Diagram illustrating synpasis between chromosomes in which the genes are not identical. In the lower chromosome it will be noted that deletion has occurred involving genes *j*, *k*, and *l*. This portion of the upper chromosome is drawn to one side so that the paired genes match exactly (page 392). (*Shull.*)

determining an altered gene complex in either member of the synaptic mates. If some of the genes in one of the pairing chromosomes are out of place or if they are missing, then the corresponding or alternative genes in the normal chromosome cannot join in synapsis. Accordingly, this region of the normal chromosome pulls away from the abnormal

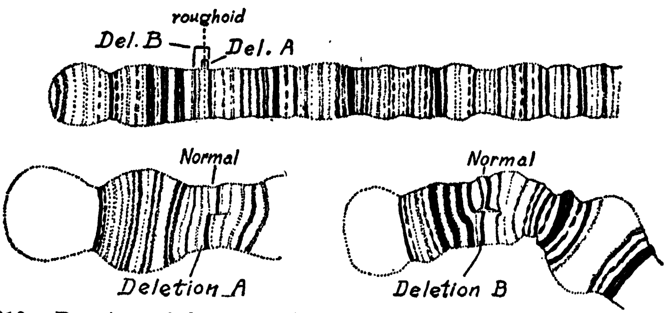


FIG. 210.—Drawings of the terminal portion of one of the giant chromosomes (II), salivary gland cell, Drosophila, showing actual deletion as diagrammed in Fig. 209. The normal condition of synapsis is shown in the upper figure. The affected region, which carries the genes for *roughoid*, an eye character, is indicated at *Del. A* and *Del. B*. Modification in synapsis as the result of the deletions is shown at a maximum magnification in the lower figures. In *Deletion A* one of the synapsing chromosomes is normal, whereas one band is missing from the other. In *Deletion B*, one chromosome is normal and three bands are missing from the other one. (*Painter*, "*Science in Progress*," *Yale University Press.*)

synaptic mate and forms a loop-like structure off to one side, and this permits those genes which are present and normally located in both chromosomes to meet in synapsis. The synaptic behavior of the normal chromosome gives visible evidence to the cytologist of regions with an altered gene arrangement in the synaptic mate. Intensive study of the latter, particularly in the giant chromosomes, has brought

altered heredity patterns almost down to the actual genes concerned (page 335). (Figs. 209 to 211.)

We have just been dealing with mutations that involve areas in the chromosomes of sufficient size to be observed under the microscope. Mutations occur, however, in which the chromatin pattern of the mutants shows no visible alteration even under the highest magnifications. Such mutations must have their sole basis in the chromatin complex, but they may result from a change in only a single gene and, therefore, cannot possibly be brought within the limits of microscopic visibility. Such mutations are said to be due to point changes, the point being the exact region in the chromosome at which

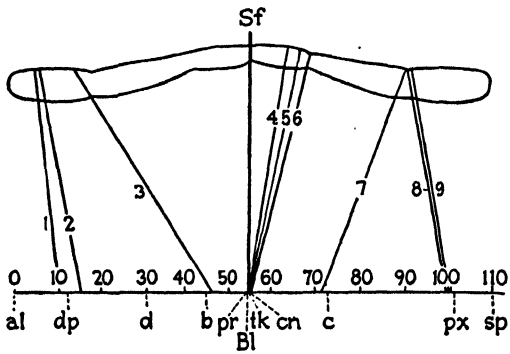


FIG. 211.—Diagram illustrating the determination of gene loci by different methods. *Above* is shown an outline drawing of Chromosome II. *Below*, the chromosome map of this chromosome is given, with the positions of several gene loci indicated. The positions of the genes in the chromosome map have been determined by data from matings involving crossovers (page 387); the positions of certain of these genes have also been determined by cytological studies following translocation (Figs. 207, 208). It will be noted from the positions of the vertical lines (1 to 9) that genetical and cytological data agree in the order of gene loci but indicate certain differences in the distances separating them. *Sf*, spindle fiber attachment; *Bl*, bristle· *dp*, dumpy—a body character; *b*, black; *sp*, speck—color on wing, etc. (*After Dobzhansky. Redrawn.*)

the mutating gene is located. It is impossible to speak with absolute certainty, but it appears most likely that, in a point change, an actual chemical change takes place in the mutating gene. In the final analysis, a gene can be nothing more or less than the tiniest bit of a specific chemical compound, possibly a single molecule. In addition to point changes as the result of chemical change, the possibility also exists of a mutation due to a change in the position of a gene or genes, the so-called *position effect*. In other words, the mutation may be due to a change in the position of a gene rather than a change in its chemical nature. Considerable evidence has been very recently accumulated that indicates the importance of gene position. The possibilities involved may be visualized by realizing the changes that would follow

the removal of a factory manufacturing chemicals from one town to another, even though the two places might not be far apart. The importance of gene position in synapsis has just been emphasized.

The discussion of inheritance, so far presented, has been concerned with formation and transmission from generation to generation of the gene complex responsible for the characters expressed in the individual. At this point, some attention may profitably be given to the environment with which each living organism is in continuous adjustment and on which it depends for a constant supply of the materials essential

FIG. 212.—Photograph of a corn field showing plants growing under favorable environmental conditions (left) and plants growing under unfavorable environmental conditions as the result of crowding (right). (*Woodruff, after Blakeslee.*)

to the life processes. The question is: Do the characters shown in the mature organism depend exclusively upon the gene complex? The answer is clearly in the negative. Each individual represents the results obtained from a partnership in which the gene complex has been working in close association with the environment. If the environment is favorable, the gene complex will come to full fruition, but, if the environment is unfavorable, the normal group of characters expected from a particular gene complex will be restricted or modified in various ways. (Fig. 212.)

But now we come to another question with reference to environmental effects: Is the chromatin complex with its thousands of con-

stituent genes changed in the organism by the environmental factors so that gametes will be formed with an altered gene complex. The answer is "no" but with certain reservations. Thus, the geneticist has discovered that if the immediate environment of Drosophila contains X rays of certain strength, the chromatin in the germ cells will be altered (page 339). In this connection it was suggested some years ago, following the discovery of the cosmic rays with their great power of penetration, that possibly these rays had been directly affecting the chromatin of organisms from the earliest times.

However, the condition just considered, in which the biologist has used X rays to penetrate directly to the germ cells and alter the normal chromatin pattern, is very different from environmental effects which affect only the somatic cells. In such cases, if the heredity of the succeeding generations is to be changed by environmental action, it would be necessary for the chromatin changes in the affected somatic cells to be transferred to the gene complex in the gametes and correspondingly to modify the gene pattern in them. Suppose, for example, the somatic cells present in the thyroid gland of a particular individual are subjected to an unfavorable environment as the result of a greatly decreased iodine content in the blood stream, the latter, in turn, being due to faulty nutrition. In time, an abnormal condition of the thyroid develops. There is no reason to suppose that this environmental effect directly affects the germ plasm of the individual in any way whatsoever, and, since the gene complex of the individual remains unchanged, there appears to be no possibility of the hereditary transfer of the thyroid goiter to later generations. The unsuitable environment results merely in an individual modification that is doomed to extinction with the passing of the individual concerned. So far as the biologist can see, the same result, namely, unchanged heredity, is to be expected from all sorts of individual modifications that appear in the soma following exposure to abnormal environmental influences. (Fig. 207.)

As late as the beginning of the second decade of the present century, it was not possible to discuss evolution[1] with any authority because a knowledge of the underlying mechanism responsible for the production of new types was not available. It was clear that species had changed, that new ones had developed, but the functioning of the mechanism responsible for the tremendous variety of living forms coming from a common life stream was not known. To the paleontologists busily engaged in discovering, collecting, and mounting the fossil remains of plants and animals, the Lamarkian doctrine of the inheritance of

[1] Consult Appendix: Organic Evolution.

acquired characters still persisted with almost undiminished power. To the biologist of today, however, it is clear that successive generations of giraffes could continue to stretch their necks, in order to secure the more plentiful food supplies at the tops of tall trees, for billions of years without in any way affecting the genes responsible for the length of the neck.

The crux of the matter was stated by Professor E. G. Conklin a few years ago when he wrote that "The germ cells are the only living bonds not only between generations but also between species, and they contain the physical basis not only of heredity but also of evolution." Any evolution that has occurred in the past, therefore, has occurred as the result of the same mechanism that will bring it about today, namely, changes in the germ plasm. The geneticist and the cytologist have made clear the main features responsible for variations in the germ plasm[1] and, in addition, have been able to link these microscopic changes involving the genes in the chromosomes directly with visible alterations in the resulting offspring. From the material presented in the two preceding chapters, it is apparent that the condition of our knowledge in this field at the end of the third decade of this century is very different from that a few years earlier, for we do have a knowledge of the underlying mechanism responsible for the production of new types. It is the same mechanism that is responsible for the production of each new individual.

[1] Consult Appendix: Germ Plasm.

CHAPTER XV

HUMAN HEREDITY

The knowledge gained from the consideration of reproduction and heredity in the preceding chapters can now be used as a basis for an inquiry into the established facts relative to inheritance in the human organism. Human heredity has long been a subject of the keenest interest, with the result that a great amount of data has been accumulated. For the most part, however, the earlier data rest upon upon observations of a more or less random nature which were not subject to rigid scientific scrutiny. With the establishment of the Mendelian laws and the realization of their universal application in the living world, geneticists everywhere have given increasing attention to the collection and correlation of data that would throw light upon the behavior of the genes in human germ plasm in determining the characters of the offspring. As a result, a considerable number of characters have been found in man that are known to be transmitted to offspring in accordance with the established Mendelian laws. Two of these characters, namely, the inheritance of sex and the inheritance of a sex-linked character, color blindness, have been discussed in the previous chapter. (Fig. 202.)

It should be emphasized that the difficulties inherent in securing accurate knowledge of human heredity are very great. In the first place, the geneticist has no control over the matings; he can only sit on the side lines and observe the results. Then, too, observations are possible only on the characteristics of a comparatively small number of offspring extending over a few generations. Information regarding the previous generations of a family is rarely a matter of written record unless it be concerning the occurrence of some particularly striking characteristic, usually abnormal in nature. On the whole, then, the data regarding the ancestors of a particular couple are apt to be sketchy and hearsay rather than detailed and accurate. Nevertheless, considerable reliable information relative to human heredity is now at the disposal of the geneticist, and the inheritance of a variety of characters in man well established. Primarily, it should be recognized that the analysis of the relatively unsatisfactory data dealing with human heredity and the recognition of the general applicability

of the Mendelian laws would not have been possible except for the results obtained by the geneticist from controlled breeding experiments in a wide variety of organisms. In our present examination of Mendelian inheritance in man, it will be possible to consider the inheritance of only relatively few characters but sufficient, perhaps, to show the broad application of the principles that have been thoroughly established in various other organisms. The inheritance of pigmentation, eye defects, skeletal characteristics, and blood groups are suited for our present discussion and will be considered in the order named, following which consideration can be given to certain general problems associated with human hybridization. (Fig. 213.)

INHERITED CHARACTERISTICS

Pigmentation.—It has become evident that the visible pigmentation of all degrees and colors present in the eye, skin, and hair of the white, yellow, or black races results from the presence of varying amounts of two basic pigments, melanin and carotene, which are formed by, and remain in, the cytoplasm of various types of cells. Presumably the presence of the gene or genes responsible for pigment formation results primarily in the formation of a specific enzyme, and the latter works in association with a pigment-forming substance (chromogen) in the cell cytoplasm. Occasional instances in which blue eye color is associated in an individual with heavily pigmented, or brunette, skin and hair give good evidence that separate genes are responsible for the production of pigment in these three structures, but the method of pigment formation is believed to be the same in each instance. In the case of melanin, which is a widely distributed brown pigment, the chromogen has been identified as the amino acid tyrosine, normally present in cytoplasm. The reaction between tyrosine and a specific enzyme, tyrosinase, forms melanin. (Plate XVII, page 415.)

The other human pigment, carotene, is yellow in color and is found in both plant and animal cells. It is particularly prominent in the carrot from which it derives its name. Presumably, a specific enzyme (not as yet isolated) which functions in association with a cytoplasmic chromogen is necessary for its formation. Carotene has recently become of increasing interest because of its close relationship to vitamin A (page 58). The latter, in turn, is associated with night blindness and other pathological conditions of the eyes and is required for the formation of the visual purple in the retina of the eye. Carotene is regarded as the mother substance of vitamin A. The actual synthesis of the latter occurs in the liver cells.

In rare cases, a hereditary defect, albinism, results in the absence of both pigments. Albinism behaves as a simple Mendelian recessive. Accordingly, all the children of albino parents, since the latter must be homozygous to show the defect, are albino. With both parents normally pigmented, but carrying the recessive gene for albinism, 25 per cent of the offspring would be expected to show the defect as in a typical monohybrid. The examination of data from a considerable number of families has shown this percentage to be about 29. It is not clear why it should be considerably in excess of the expected ratio.

Human skin color may vary from the deepest black to the purest white, with a wide intermediate range of browns, tans, and yellows between these two extremes. The pigmented cells of the skin, for the most part, are found in the epithelial cells, but they are present to some extent also in the outer layers of the underlying dermal cells. The offspring from unions of homozygous colored individuals and homozygous whites show an intermediate, or mulatto, condition with respect to skin color. Children of the hybrid mulattoes show varying degrees of color ranging from deep black, as in one of the grandparents, to clear white as in the other grandparent.

Consideration of data involving a large number of F_2 children from mulatto marriages shows that about 6 per cent are deep black. Essentially the same percentage is white-skinned. This clearly indicates a multiple gene condition in which two pairs of genes determine the pigmentation of the skin. Thus a dihybrid condition for color is believed to be present as in the brown-seeded grains, described in the previous chapter (page 372). Other authorities have accumulated evidence indicating that a trihybrid condition with three pairs of genes is associated with human skin color. It is also clear that the production of pigment in the skin of individuals is directly associated with sunlight. The temporary coloring, or tanning, of the skin, following repeated exposures to sunlight, is a matter of common observation, as is also the formation of freckles. It is also noteworthy that skin pigmentation, even in the children of the colored races, is much reduced at birth. (Fig. 194.)

Hair Qualities.—Possibly wider variations are found in hair color than in either the eye or the skin; for in the white race, all gradations from deep black to a very light yellow or flaxen and branching off to a decided red are of normal occurrence. It appears that red hair color is due to a special derivative of the carotene pigment, whereas all the other shades have their origin in varying proportions of the melanin and carotene pigments. The absence of both pigments gives the abnormal albino condition noted above. Failure to produce hair

Inherited Characters in Man

1. *Blending*

General body size, stature, weight, skin-color, hair-form (in cross-section, correlated with straightness, curliness, etc.), shape of head and proportions of its parts (features).

2. *Mendelian*

	Dominant	*Recessive*
Skin and hair	Dark.	Blonde or albino (probably multiple allelomorphs).
	Spotted with white.	Uniformly colored.
	Tylosis and ichthyosis (thickened or scaly skin).	Normal skin.
	Epidermolysis (excessive formation of blisters).	Normal skin.
	Hair beaded (diameter not uniform).	Normal hair.
Eyes	Front of iris pigmented (eye: black, brown, etc.).	Only back of iris pigmented (eye blue).
	Hereditary cataract.	Normal.
	Night blindness (when not sex limited).	Normal.
	Normal.	Pigmentary degeneration of retina.
Skeleton	Brachydactyly (short digits and limbs).	Normal.
	Polydactyly (extra digits).	Normal.
	Syndactyly (fused, webbed, or reduced number of digits).	Normal.
	Symphalangy (fused joints of digits, stiff digits).	Normal.
	Exostoses (abnormal outgrowths of long bones).	
	Hereditary fragility of bones.	Normal.

FIG. 213.—Showing the behavior of various characters which are known to be

	Dominant	*Recessive*
Kidneys	Diabetes insipidus (excessive production of urine).	Normal
	Normal.	Alkaptonuria (urine black on oxidation).
Nervous system	Huntington's chorea.	Normal.
	Normal.	Hereditary feeble-mindedness.

3. *Mendelian and Sex-Linked*

(Appearing in males when simplex, but in females only when duplex.)

Normal.	Gower's muscular atrophy.
Normal.	Haemophilia (bleeding).
Normal.	Color blindness (inability to distinguish red from green).
Normal.	Night blindness (inability to see in faint light).

4. *Probably Mendelian but Dominance Uncertain or Imperfect*

Defective hair and teeth or teeth alone, extra teeth, a double set of permanent teeth, hare-lip, cryptorchism and hypospadias (imperfectly developed male organs), tendency to produce twins (in some families determined by the father, in others by the mother), left-handedness, otosclerosis (hardness of hearing owing to thickened tympanum).

5. *Subject to Heredity, but to what Extent or how Inherited Uncertain*

General mental ability, memory, temperament, musical ability, literary ability, artistic ability, mathematical ability, mechanical ability, congenital deafness, liability to abdominal hernia, cretinism (due to defective or diseased thyroids), defective heart, some forms of epilepsy and insanity, longevity.

heritable in man. *(Castle, "Genetics and Eugenics," Harvard University Press.)*

pigment in the later years of life results in grayness. Not uncommonly, premature grayness appears as a definite hereditary character. The factors for human hair color have not been determined as definitely as they have in the case of the eyes and skin, but a very great deal of work has been done upon the inheritance of hair color in various other mammals. In the rabbit, to take a well-known example, it is found that no less than four pairs of genes are concerned with the development of hair color. Speaking in general terms, the results show that darker shades of hair color tend to dominate over the lighter shades in inheritance.

In addition to wide variation in color, the character of human hair differs markedly with respect to form. Straight, curly, kinky, coarse, fine, short, and long are terms commonly used to describe various hair types. Each of these has its basis in the distinctive shape and character of the hair follicles, and the latter, in turn, is the product of the gene complex (page 191). Again, some types of hair grow for a short time and are shed while very short; other varieties are retained for long periods and grow to great lengths. A certain type of baldness in the human male, known as *hereditary*, or *pattern baldness*, presents an interesting type of inheritance in which the genes producing this condition are influenced by the sex chromosomes, though not directly linked with them, and so we have sex-influenced characters as well as sex-linked characters (page 380). The underlying fact in the hereditary transmission of a sex-influenced character is that identical genotypes produce different phenotypes in the two sexes. Thus in the case of hereditary baldness, the heterozygous condition (*Bb*) results in baldness in the male where it acts as a dominant but not in the female where it acts as a recessive.

Eye Color.—The inheritance of eye color in man has been the subject of much interest, particularly since the establishment of the Mendelian laws. An examination of the iris shows that pigmented epithelial cells containing melanin particles may be present both in front and in back of the eyes. This double pigmentation, or *duplex* condition, produces brown eyes. In a so-called *simplex* eye, the melanin is found only in cells located at the back of the iris. The reflection of the light rays in the simplex eye from the anterior unpigmented tissues of the iris gives blue eye color. In the albino condition, no pigment is present in any region of the iris, and the pinkish eye color results from the reflection of the blood in the iris vessels. Consequently, the albino iris offers very little protection to the sensitive retina cells from the incoming light rays, and the affected individual finds it necessary to keep the eyelids partially closed.

In general, it is found that the brown-eyed condition is dominant over the reduction of pigment that gives blue eyes. On this basis, two types of brown eyes occur; one being homozygous, and the other hybrid carrying a recessive gene. The various possibilities of inheritance from the mating of the two types correspond to those shown in the monohybrid square. The results obtained from a study of eye color in a large number of Danish families have shown close conformity to expected Mendelian ratios (page 361). However, it is recognized also that various other factors are often bound up with inheritance of eye color and, when present, greatly complicate the analysis. Thus, pigmented cells carrying the yellow carotene sometimes occur in the iris. Also, partial pigmentation in the front wall of the iris results in scattered specks or streaks or even a complete ring of color. The control of this additional pigmentation is undoubtedly lodged in other genes—thus giving a multiple gene condition for eye color.

Eye Defects.—The inheritance of various eye defects, both structural and functional in nature, have been studied by various investigators. In the previous chapter, one of the most interesting of these, color blindness, was used as an example of sex-linked inheritance (page 382). Altogether, the inheritance ratios have been studied for some 20 different eye abnormalities, including such structural defects as displacement of the lens, opacity of the lens (cataract), and partial or total absence of the iris. Among the functional defects (all of which, of course, have a structural basis of some kind) are color blindness, shortsightedness, night blindness, degeneration of the optic nerve (Leber's disease), degeneration of the retina, and paralysis of the eye muscles. The last defect has appeared as a recessive character in the offspring of cousin marriages. Undoubtedly the most data have been collected bearing on the inheritance of the shortsighted (myopic) condition, night blindness, and color blindness.

In connection with myopia, which is one of the least serious of the various eye defects, the study in Berlin, a few years ago, of over 900 family histories showed that the character behaved in all cases as a Mendelian recessive but that more than one pair of genes were involved in producing the defect. Night blindness, which is due to a defect in the visual cells of the retina, has been traced through 10 generations of the Nougaret family in France by the study of more than 2,000 case histories. The results clearly show that the defect was inherited in this family as a simple Mendelian dominant. Much less complete records of other families in the United States give evidence that the defect may be sex-linked. It is apparent from the examples cited that no general statement can be made to cover the inheritance of human

eye defects, for they may be recessive or dominant or sex-linked, and also considerable evidence indicates that inheritance of the same type of defect is not uniform in different families.

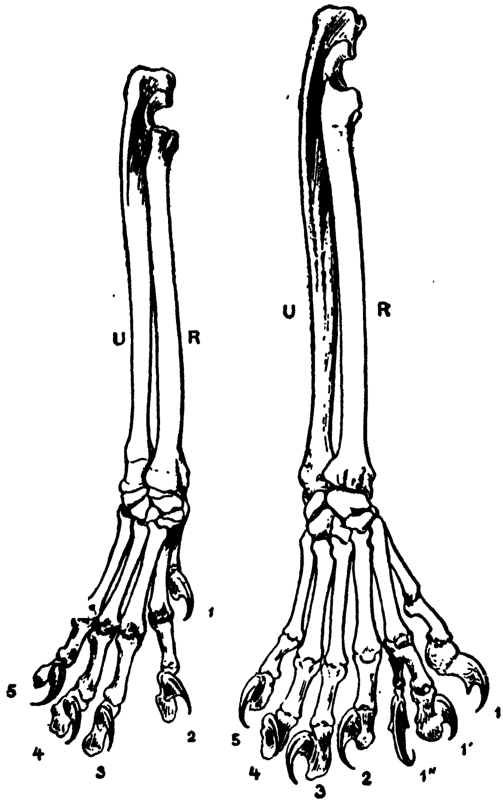
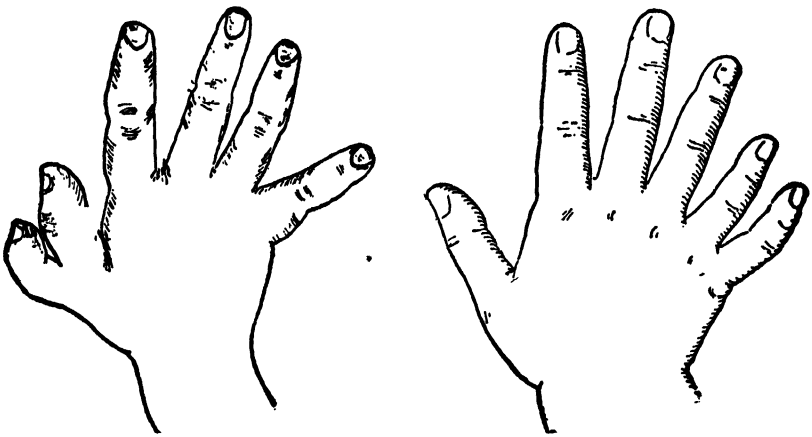


FIG. 214.—Portion of the skeleton of the cat's forelimb. *A*, normal condition; *B*, polydactylous condition as a result of mutation producing twinning of certain digits. (*Coe, "Evolution of Earth and Man," Yale University Press.*)

Skeletal Characteristics.—The inheritance of defects in skeletal structures has been mostly studied in the bones of the hands and feet. The departures from the normal gene complex may result in the occurrence of extra digits (polydactyly) or the opposite extreme in which a complete absence of hands and feet occurs, as has been recorded in the members of one Brazilian family. In addition to polydactyly, fairly frequent examples are found in which the number of digits has been reduced through a fusion of the bones (syndactyly). In other cases, a webbed condition in the hands or feet is inherited. This latter defect is due to the persistence of a web of skin tissue between the digits,



A B

FIG. 215.—Illustrating human polydactyly. *A*, heritable mutation producing twinning of thumb; *B*, twinned little finger produced apparently as a defect in development and, therefore, not heritable. (*Coe, "Evolution of Earth and Man," Yale University Press. After Milles.*)

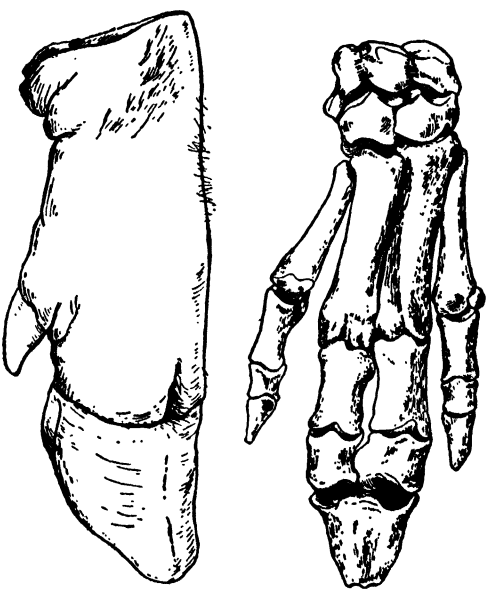


FIG. 216.—Drawings showing external structure (left) and also the skeleton of the foot of the "mule-footed" pig. This condition is produced by a mutation which produces a fusion of the terminal phalanges and the hoof covering this region. (*Coe, "Evolution of Earth and Man," Yale University Press.*)

usually the second and third, and is not a skeletal defect. Finally, an abnormally short type of digit (brachydactyly) occurs, in which one joint is missing from each digit, that appears as a hereditary character. The data from a large number of individuals show that skeletal defects, with certain exceptions, behave as simple Mendelian dominants. The presence of a skeletal mutation in an individual is, therefore, very good evidence that the defect will be transmitted to the next generation. (Figs. 213 to 216.)

Galton and the Principles of Biometry

The studies of Galton on human inheritance are probably the most thorough of any of the pre-Mendelian studies, and his "Laws of Ancestral Heredity," published in 1897, just a few years before the rediscovery of Mendel's results, were considered of the highest importance by biologists in the early years of the present century. But Galton's laws have not continued to be of major importance because he failed to recognize the particulate nature of inheritance based upon the gene mechanism (page 355). Nevertheless, Galton has a great deal to his credit. He was the first to distinguish between alternative and blending inheritance. An example of the former was found in the inheritance of hair color in Basset hounds and of the latter in human stature. From his extended and thorough studies on the inheritance of stature, or tallness, in man, Galton established the principles of biometry, the measurement of living things.

Biometrical data, correlated in accordance with mathematical formulae developed by Pearson, have proved to be of the greatest importance in statistical studies of variation in heredity. Since, as shown earlier, the inheritance of various characters in which multiple genes are concerned results in a graded series of variations in the offspring, the answers to the problems involved require the determination of the characteristics of a large population rather than of an individual (page 376). Biometrical methods must be used. The inheritance of stature is a very good example. If a large number of individuals are measured for height, it will be found that a small percentage are very short, a corresponding number are very tall, but the heights of most of those measured fall between these two extremes. Thus, for example, in a certain population, the extremes for height might be found to be 58 and 76 in., with the greatest number measuring around 67 in. From the data thus secured, a curve can be constructed that will show the results graphically. The same methods were applied in determining the inheritance of color in the brown-seeded oats, described in the previous chapter, through the examination of large numbers of seeds

and establishing the percentages with respect to the amount of color present. In this case, the two extremes were very dark-colored seeds

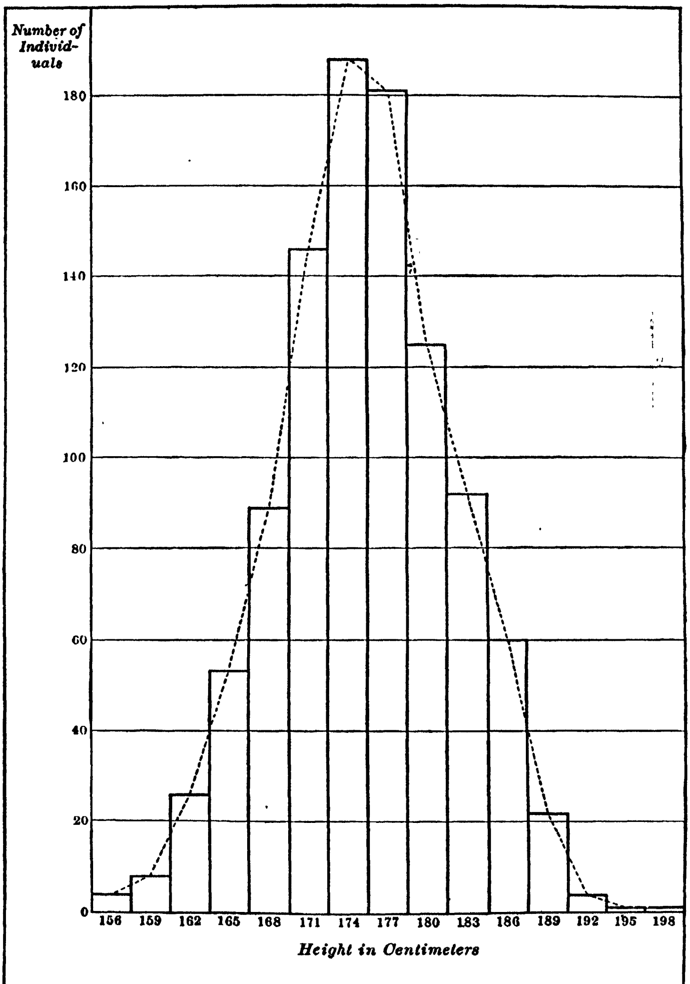


FIG. 217.—Illustrating variation in heights of 1,000 Harvard students, ages 18 to 25. The curve (dotted line) is computed from the number of individuals at a particular height. (*Castle, "Genetics and Eugenics," Harvard University Press.*)

and seeds with no color. Each of these was found to comprise about 6 per cent of the total population. The greatest percentage of seeds was found to be intermediate in color, from which they graded toward

the dark and toward the light-colored. The percentages obtained gave the clue to the number of genes involved (page 372). (Figs. 217, 218.)

There is every evidence that height, general body build, shape of head, and various other body characters are determined by multiple genes. But in some instances, there is also evidence of alternative

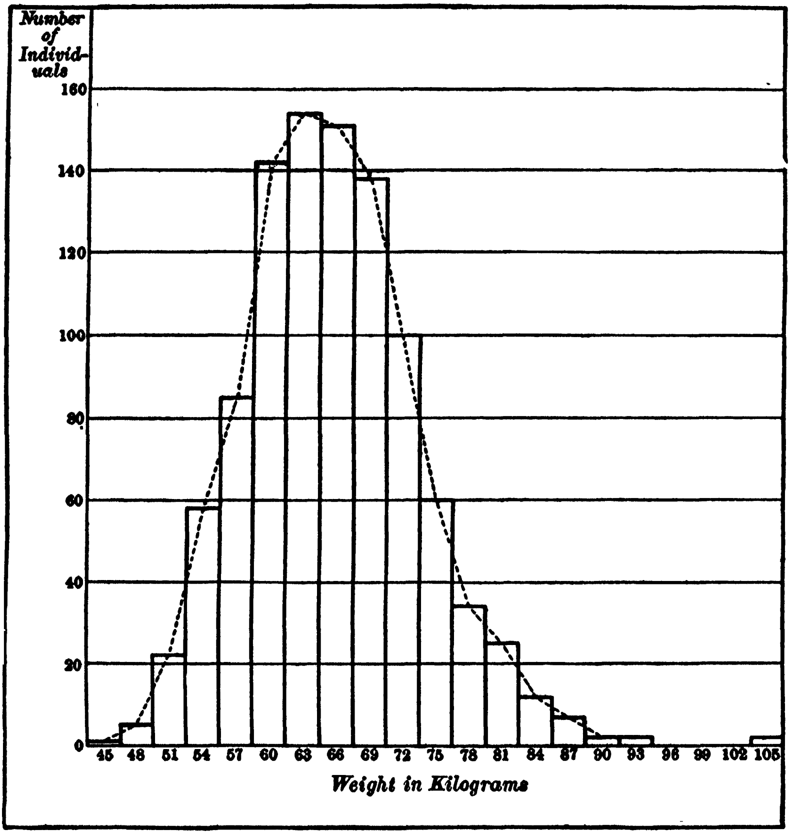


FIG. 218.—Illustrating variation in weights of 1,000 Harvard students, ages 18 to 25. *Cf.* Fig. 217. (*Castle, "Genetics and Eugenics," Harvard University Press.*)

inheritance. In the inheritance of stature, for example, some data show that the progeny from matings of tall and short individuals tend to be below the average in height, which indicates that the genes for shortness are dominant, to some extent at least. But the problem is even more complicated because the size of the vertebrate body is markedly affected by hormonal action. This is well shown in the gigantism resulting from hyperactivity of the pituitary gland or in

dwarfing that results from other hormonal factors (page 113). Hormonal action, in turn, is directly influenced by environmental conditions. The failure of the environment to provide iodine in the food will produce a cretinous condition, no matter what the gene complex of the individual happens to be (page 106).

Blood Groups.—Nearly forty years ago, it was discovered that a very serious reaction, which resulted in the sticking together, or agglutination, of red blood corpuscles, took place when blood from certain individuals was mixed. Later it was shown that the agglutination of the red cells was not a haphazard phenomenon, that there were four types of blood found in man, now known as Groups *A*, *B*, *AB*, and *O*, and that the agglutination reaction always occurred when certain groups were mixed. Extensive investigation has shown that agglutination depends upon the presence of two blood substances: the antigen, carried in the red blood cells; and the antibody, carried in the serum (page 166). Agglutination requires the presence of the antigen and its specific antibody. Both antigen and antibody cannot, of course, be present in the blood of the same individual for, if they were, agglutination would occur. The condition of the various types of blood may be summarized as follows:

Group *A* carries antigen *A* and antibodies for Groups *B* and *AB*.

Group *B* carries antigen *B* and antibodies for Groups *A* and *AB*.

Group *AB* carries antigen for the three other groups but lacks antibodies. It will be agglutinated by any of the other groups. Group *AB* individuals are undesirable as blood donors.

Group *O* lacks antigen but carries antibodies for the three other groups. It will not be agglutinated by any of the other three groups. Group *O* individuals are important blood donors. (Fig. 219.)

Genetical studies have brought the data from the inheritance of the different blood groups into line with the Mendelian principles by the establishment through experimental breeding of a method of inheritance that involves an extension of the Mendelian laws beyond those considered in the previous chapter. This condition may be explained in a few words by the statement that the paired genes (allelomorphs) for a certain character may be present in different varieties or forms in the various individuals of a population. Instances of this genic variation have been demonstrated, for example, in the genes for certain eye colors in Drosophila and also in hair color in the rabbit. The data there obtained fit with that of human blood group inheritance which can now be stated.

In the transmission to offspring, one may say that the genes for Group *A* act as a dominant, Group *O* as a recessive, and Groups *B* and

AB are intermediate. If the dominant gene associated with the blood groups is designated as *A* and the recessive designated as *a*, then, just as in a typical monohybrid, Group *A* individuals may occur either as pure dominants with the genotype *AA* or as hybrids with the genotype

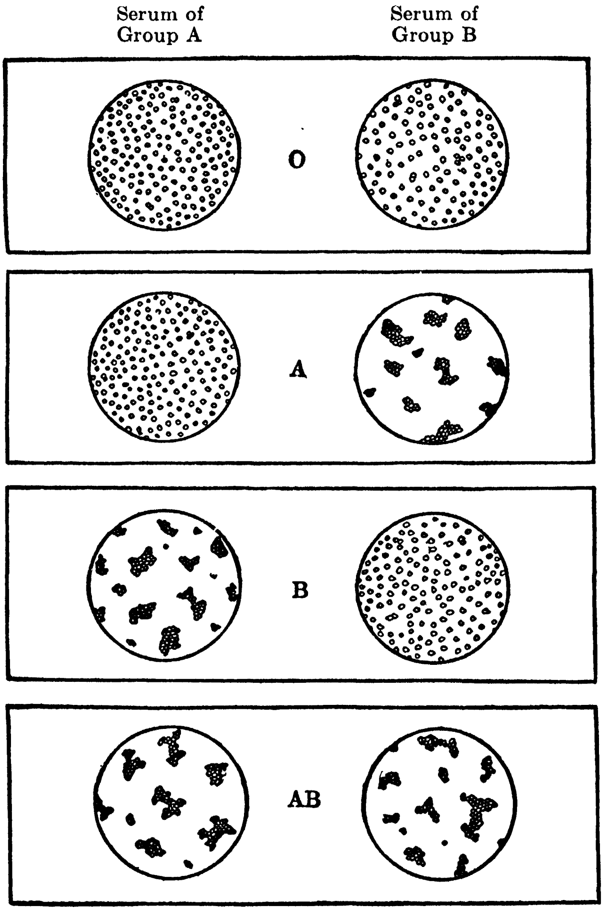


FIG. 219.—Illustrating the technique for determining the blood group to which the blood obtained from a particular donor belongs. "Two drops of serum, one of Group *A* and one of Group *B*, are put on a glass slide and a bit of the unknown blood placed in each. If the red blood cells agglutinate in one (*A* or *B*) or both (*AB*) or neither (*O*), the group of the unknown blood is determined in accordance with the scheme illustrated." (*Shull, modified from Snyder, "Blood Grouping," The Williams & Wilkins Company.*)

Aa. All Group *O* individuals act as pure recessives with the genotype *aa*. Now in the individuals belonging to Group *B* and *AB*, the paired genes determining the blood group are present in a different form which, for convenience, may be indicated as *a'*. The homozygous

Group B individual has the genotype $a'a'$, and the hybrid Group B has the genotype $a'a$. All Group AB individuals are hybrid and have the genotype Aa'. If now the groups and genotypes are arranged in tabular form, it will be possible to note the genotypes and the corresponding types of gametes produced.

(XXI)

Blood group	Genotypes	Gametes
A	AA	A
	Aa	A a
B	$a'a'$	a'
	aa'	a a'
AB	Aa'	A a'
O	aa	a

In addition to their basic importance in making the highly valuable blood transfusions possible, the methods used in determining blood groups are sometimes important in medicolegal work for establishing parentage. In approximately one-third of the cases involving the question of parentage it is possible to speak with authority.

Using the various gametes in the square (XXI) will show the various possibilities with regard to inheritance. Let us analyze two or three of the possibilities. Thus it can be shown that, if one parent belongs to Group A and the other to Group B, it is possible for a child to belong to any of the four groups. Obviously both of the parents in such a case must be hybrids, for the mating of a homozygous AA and a homozygous $a'a'$ could give only children with the genotype Aa' and belonging, therefore, to Group AB as shown in the square:

(XXII)

Sperm \ Eggs	a'
A	Aa'

With heterozygous A and B parents, each producing two types of gametes as shown above, the children may belong to any one of the four groups as follows:

(XXIII)

Eggs / Sperm	a	a'
A	Aa	Aa'
a	aa	aa'

Again it is evident that, if the mother belongs to Group A and the child belongs to Group B, then the father cannot belong to Group O. Thus, if the father belongs to Group O and the mother is homozygous, as AA, then the child will have to be Aa, or a member of the A group as indicated:

(XXIV)

Eggs / Sperm	A
a	Aa

If the mother is heterozygous, or Aa, the children will have to be either Group A (Aa) or Group O (aa):

(XXV)

Eggs / Sperm	A	a
a	Aa	aa

Thus it is shown that the association of a Group A parent and a Group B child excludes the other parent from Group O. Likewise, it can be established that the other parent cannot be a member of Group A.

Numerous other patterns for blood-group inheritance are established that we cannot take the space to analyze, but a few words should be said with reference to the possibility of establishing a relationship between blood type of child and father. The blood-group methods cannot, of course, definitely establish that a particular individual is a parent of the child in question. All that can be said is that certain combinations of the blood groups of one parent and child make it either possible or impossible for a member of a particular blood group to have been the other parent. To cite a few more instances, if both the parents have Group O as their blood group, it is impossible for the children to belong to any other group. With one Group O parent and one Group A parent, the child cannot belong to either the B or the AB groups. If the mother and child are both type O, then the father cannot belong to group AB. Conversely, type AB in both mother and

child excludes type O as the male parent. Even closer restrictions of relationship have been brought about by the discovery of two additional antigens and the establishment of the M and N blood groups.

That the genes for a particular character, which necessarily lie in the same chromosome position, may be found in more than one form, as indicated by a and a', is not surprising from the chemical standpoint when it is realized that a very slight change in the position of an atom or atoms in a molecule may result in the production of a different substance with distinctive characteristics. Various results have shown that a gene for a particular character may exhibit four or even more varieties. Technically, this condition of gene variety is known as *multiple allelomorphs* (multiple alleles). Careful distinction must be made between the *multiple genes* condition, which involves separate pairs of genes as in seed color, and the *multiple allelomorphs*, which are concerned with different varieties of a single pair of genes as just shown in the blood groups. Furthermore, it must be understood that an individual can never form gametes that carry more than one variety of a particular allelomorph. Thus the gametes determining the blood groups carry either A or a or a' but never any combination of these. Accordingly, not more than two allelomorphic varieties are ever present in the resulting zygote and the mature individual. The latter, for example, may be AA, Aa, or Aa', as shown in the table above, but never Aaa'. (XXI.)

Human Hybridization.—The various races of Man inhabiting the world today belong to one genus, *Homo*, and one species, *sapiens*. The most widely diverse human types interbreed and produce fertile offspring. The ability to interbreed and to produce fertile offspring has long been recognized as one of the most decisive characteristics in the determination of a distinct species. Modern knowledge of the specificity of the chromatin complex, as shown in the previous discussions, has added additional prestige to interbreeding as a species limitation (page 334). In general, it is found that two individuals belonging to widely separated species cannot produce offspring; individuals from species that are more closely related may produce offspring, but the latter are usually infertile as shown by the mule. The production of fertile offspring represents an even closer relationship, and the individuals participating must possess homologous chromosomes bearing the same gene complex. Accordingly they may be assigned to membership in a common group, the species. Membership in a species does not mean absolute uniformity by any means; different varieties, or races, are included within the species limits, and even smaller subdivisions with recognizable differences continue down

to individual differences. In the final analysis, as has often been said, no two individuals in any species are exactly alike. It may be of interest in this connection to call attention to the results obtained when two closely related species of Ungulates, the horse and the ass, are mated. The two species are fertile when mated and produce a characteristic hybrid offspring, the mule, when the male ass (jack) is mated with the female horse (mare).[1] But the hybrid mule is practically always sterile, and the reason lies in the fact that the chromatin complex is different in the two species. Gametogenesis in the mule cannot occur because homologous mates for the chromosomes received from the diverse parents are lacking; this prevents synapsis and the formation of functional gametes—the mule is sterile. However, even

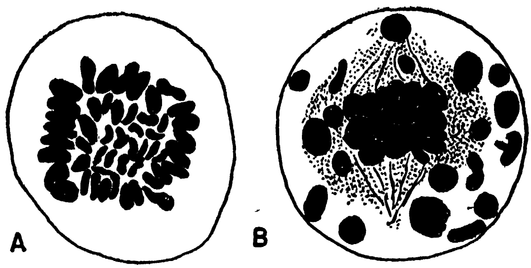


FIG. 220.—Illustrating the basis of sterility in species hybrids, as described on page 414. Chromosomes of the mule in the developing germ cells. *A*, early stage showing the maternal chromosomes of the horse (large) and the paternal chromosomes of the jack (small); *B*, later stage of germ cell formation showing degeneration of chromatin due to the inability of the chromosomes to pair in synapsis with homologous mates. (*Jennings, "Genetics," W. W. Norton & Company, Inc. After Wodsedalek.*)

though sterile, the mule has been found to be a very desirable hybrid type because of its strength and high resistance to unfavorable conditions. (Fig. 220.)

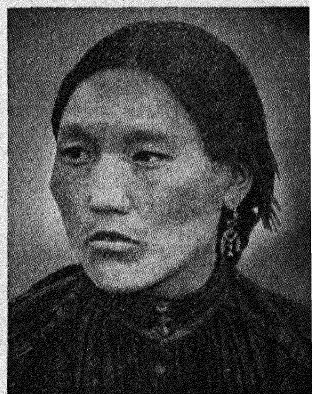
The human species, *Homo sapiens*, as seen in the world today, includes three great primary subdivisions or races: the whites (Caucasian), the yellow-browns (Mongolian), and the blacks (Negroid). Chief subdivisions of the Caucasians include the Nordic, Alpine, and Mediterranean peoples; subdivisions of the Mongolians include the Mongolic (Chinese and the Japanese), the Malay, (Hawaiians and other South Sea Islanders, American Indians, and Eskimos); subdivisions of the Negroid race include the Negroes proper and a diverse group, the Pygmies. These various peoples have long since ceased to exist as completely segregated groups. Almost every conceivable racial mixture has occurred at one time or another during the thousands

[1] Essentially the same condition obtains with the reciprocal cross between the male horse (stallion) and the female (jenny).

1. Nordic

2. Alpine

3. Mediterranean



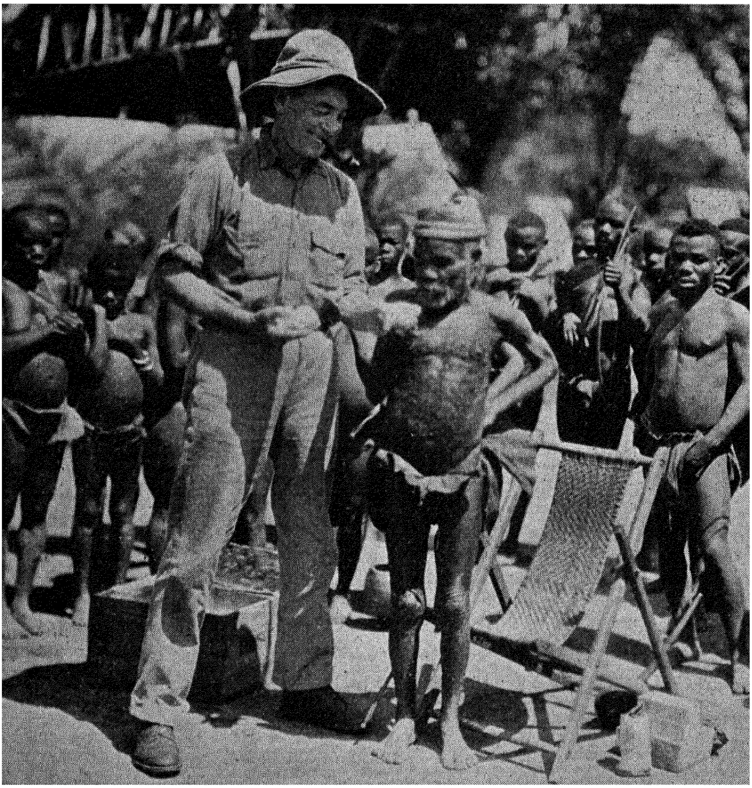
4. Mongoloid

5. Negroid

6. Half-breed (page 417.)

PLATE XVII.—Representatives of various human races. (*Baur, Fischer, and Lenz, "Human Heredity," George Allen & Unwin, London.*)

of years that *Homo sapiens* has roamed the earth, and, so far as the scientist is aware, there are no barriers to the production of fertile offspring from the union of individuals from even the most diverse races. Well-authenticated examples of human hybridization, involving considerable numbers of individuals and extending over many years, have been studied by the experts in this field. A few of the more important of these may be noted. (Plate XVII; Fig. 221.)



Ewing Galloway

FIG. 221.—Photograph of the African pygmies.

The Pitcairn Islanders represent a mixture of British and Polynesian stock, which was instigated in 1790 following the mutiny on a British ship, the *Bounty*. Some of the mutineers, in order to escape punishment, made their way to the then unknown Pitcairn Island and took with them twelve native Polynesian women and six men. The descendants of the motley group, now numbering a thousand or so, occupy Pitcairn Island and the neighboring Norfolk Island as well. The racial mixture appears to have established a healthy, vigorous

stock. Many other examples of racial mixtures involving the Polynesian peoples are known, particularly in Hawaii. Thus, offspring from Hawaiian-Chinese unions give notable evidence of the establishment of a very favorable hybrid type.

Hybridization between Dutch colonists and Hottentots in Southwest Africa has resulted in the establishment of a distinct group which has held together and developed certain distinctive and, on the whole, favorable features (page 415, *6*). In many of the alternative parental characters exhibited by the very diverse parental types, it is clear that

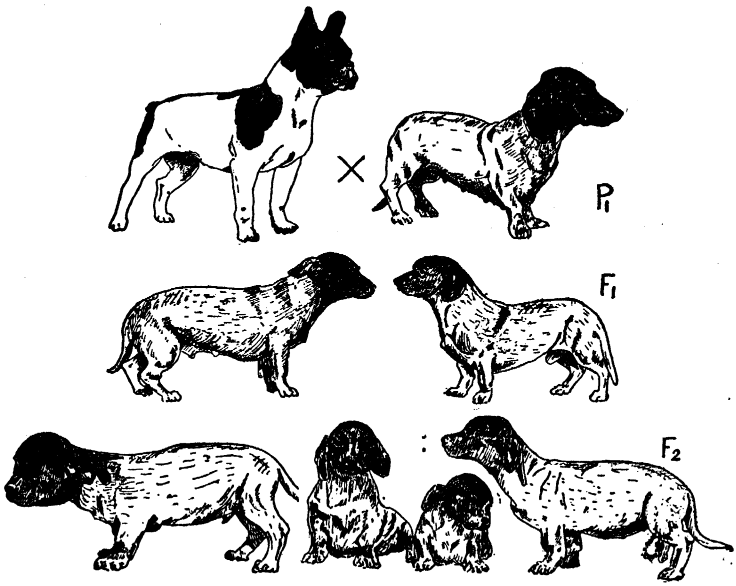


FIG. 222.—Drawings illustrating hybrids in the F_1 and F_2 generations produced by mating the French bulldog with the Dachshund. (*Stockard, "Physical Basis of Personality," W. W. Norton & Company, Inc.*)

the hybrids are intermediate. Hybridization of the native Filipino, on the contrary, produces offspring that are often notably inferior to the parental types in various respects. This hybrid degeneration is not so apparent in the physical characteristics as it is in the mental traits. Considerable data are available relative to the hereditary pattern in the offspring from crosses between the White and Negro races in North America. The hybrid individual, or mulatto, shows a blend of certain characters as in the skin pigmentation and various facial features, whereas in their general body build, the hybrids tend more toward the Negro ancestry. There appears to be no scientific evidence that sterility appears in the offspring from crosses involving less of the negro ancestry as sometimes stated.

Controlled breeding experiments with dogs have yielded interesting and important results in recent years which should be considered in connection with the problems of human hybridization. The many varieties of dogs distributed in every land are assigned to one species, *Canis familiaris*. All varieties interbreed freely and produce hybrid offspring in which many of the parental characters are clearly inherited in accordance with Mendelian laws. But the hybrid offspring from certain crosses do not appear to have assembled a very satisfactory set of characters in their composite inheritance. The original parental types are much better. There is a certain structural disharmony in the offspring of diverse races that gives, to say the least, an unprepossessing appearance. Thus, when the short-legged Dachshund is crossed with the longer legged French bulldog, the F_1 offspring are more or less

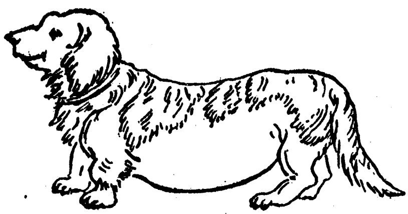


FIG. 223.—Illustrating hybrid offspring from the mating of the St. Bernard and Dachshund. (*Jennings, "Genetics," W. W. Norton & Company, Inc. After Lang.*)

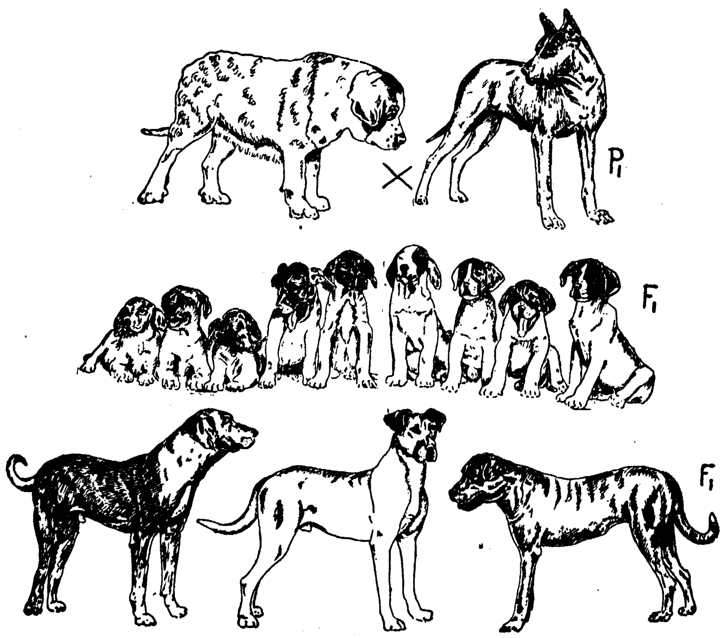


FIG. 224.—Drawings illustrating F_1 hybrids produced by the mating of the giant St. Bernard with the Great Dane. The hybrids are vigorous for the first three months, but later develop varying degrees of overgrowth, and all become paralyzed in the hind legs. (*Stockard, "Physical Basis of Personality," W. W. Norton & Company, Inc.*)

intermediate. The latter, when interbred, produce several bizarre types with ears, legs, and bodies that are far from harmonious. The segregation of these characters in the F_2 animals is in accord with Mendelian laws. Even more unsuitable are the offspring produced from matings of the very large St. Bernard and the small short-legged Dachshund. The hybrids inherit the dominant stump legs of the Dachshund in association with the long, heavy St. Bernard body. The latter hangs so low that it may even drag on the ground. An even more serious hybrid defect appears when the St. Bernard and the Great Dane are mated. A defective gene becomes apparent in this mating, which results in the partial paralysis of the offspring when about three months old. (Figs. 222 to 224.)

And so the results of the breeding experiments with a highly developed mammal, like the dog, indicates with considerable clarity that the mixing of established diverse races within the species is not always helpful and may, in fact, be decidedly harmful. Possibly the same condition applies in the case of the human organism. Various authorities are convinced that the matings of diverse types give opportunity for the production of hybrid progeny that tend to be badly assembled, as it were. The different parts of the hybrid body may not harmonize; there is lack of a unifying life architecture. This condition may not appear so serious in the first generation when many of the diverging parental characters show a blending inheritance with the production of an intermediate type. But the succeeding generations, produced by matings between hybrids, or between hybrids and either of the diverse parental types, are apt to result in the production of poorly adapted offspring as the result of the segregation of the diverse genes and the random union of the gametes.

Inbreeding

Quite the opposite of the condition just considered, with hybridization of diverse races, is of common occurrence in various plant and animal types, including man. This is inbreeding by the union of related individuals such as occurs in cousin marriages. It might be thought that, if mating between individuals belonging to diverse races has its dangers, inbreeding would be helpful. It is clear, however, that this is not always the case. Inbreeding may be helpful or harmful depending upon the genotype of the individuals concerned. If recessive genes for harmful characters lurk in the genotypes of a particular family, then the union with a related individual carrying this defective genotype is liable to end disastrously, since it will give the opportunity for the paired recessive genes coming from both

Controlled breeding experiments with dogs have yielded interesting nd important results in recent years which should be considered in duced well-endowed offspring for generations, with no hint of any undesirable characters, offers very little danger from inbreeding. This assumption, however, is not based on solid ground, for it has been shown in Drosophila that a recessive character may remain concealed in the genotype for many generations only to appear in full force in the phenotype of a certain stock when the homozygous condition is attained by the union of two gametes both carrying the recessive gene. The gist of the matter may be given in the statement that inbreeding does not produce harmful characters; it only gives an opportunity for them to be shown as somatic characters in the offspring if they are present in the parental germ plasm.

Inbreeding involving varying degrees of relationship is exhibited in the living world. The closest inbreeding occurs in self-fertilizing types of plant and animal that produce both the male and the female gametes in the same individual. This is commonly found in the plant kingdom and is not unusual among animals, as in the hermaphroditic earthworm and the parasitic flatworms. Self-fertilization may or may not be practiced in the hermaphroditic types. Earthworms go to great lengths to mate with another individual and thus to secure foreign sperm for the fertilization of their own eggs. The parasitic flatworms, on the other hand, depend upon self-fertilization.

A similar condition is found in the plant kingdom. Darwin made an extensive study of the effects of self-fertilization and cross-fertilization in a wide variety of plants and found great divergence in the different types. Some plants will not tolerate self-fertilization; that is, they are self-sterile; others utilize self-fertilization exclusively and do not appear to receive any benefit when they are artificially cross-fertilized. Wide variation in fertilization requirements exists among relatively close plant groups, as in the domesticated grains, or cereals. For example, in wheat and oats self-fertilization occurs. In fact, it is quite difficult to carry on artificial cross-fertilization in these species because the flowers are structurally adapted for self-fertilization. In corn, quite the contrary condition is found; for in this plant, cross-fertilization is essential for the production of normal progeny. The self-fertilization of corn may be forced artificially, but the plants so produced are inferior. Mendel, in his original experiments, used peas that normally were self-fertilized by pollen coming from the same flower. Self-fertilization occurring in the F_1 hybrids was a very important factor in enabling Mendel to interpret the results of his experiments correctly.

In organisms in which male and female individuals occur, as in all the higher animals, it is obvious that self-fertilization is impossible. The closest possible inbreeding occurs in matings between brother and sister or between parent and offspring. A considerable amount of experimental breeding has been directed in an endeavor to discover the results from long continued, close inbreeding. Drosophila has been inbred between brother and sister for 59 generations without producing degeneration, provided care is taken to select vigorous individuals from each generation for propagation. Likewise, inbreeding involving brother and sister matings have been studied in mammals, particularly in rats and guinea pigs, for some 25 generations and has given essentially the same result as in Drosophila. The crucial point of these inbreeding experiments lies in the selection of vigorous normal individuals in each generation to carry along the line. If parental selections are not made, defective types will increase in the population. This result is not due to the inherent harmfulness of the inbreeding for, as we have seen, self-fertilization involving the closest possible inbreeding is the accepted method in various types of plants and animals. Defective types which appear in the progeny of inbred animals result from the outcropping of recessive genes present in the closely related chromatin of the two parents. In the controlled breeding experiments, the defective individuals, homozygous for the undesirable character, are discarded and not allowed to propagate. Thus, under the experimental conditions, inbreeding aided by the selection of the most desirable individuals for reproduction tends to rid the germ plasm of undesirable recessive genes and to produce a homozygous condition carrying only desirable characters.

Suppose now that a vigorous individual from an inbred race, selected over a considerable number of generations, and therefore highly homozygous, is crossed with an individual from another homozygous race, which is not closely related. Considerable evidence exists that offspring from matings of such individuals will be more vigorous and, in general, more desirable than those obtained from continued inbreeding in either of the parental lines. This is the phenomenon of heterosis or, more commonly, hybrid vigor which is most strikingly shown in the experimental breeding of the corn plant. Strains of this plant, which have been developed by artificial self-fertilization through several generations until homozygosity is well established, will continue to produce normal progeny indefinitely, but the ears formed will be small, and the individual plants lacking in size and vigor. When two of these homozygous lines are crossed, the hybrid F_1 plants will be larger and more vigorous. And in the next

generation, grown from the F_1 seeds, a strikingly superior type of corn will always be produced. Of course, it is apparent that the unrelated homozygous parents must be desirable types and also that they should not belong to widely diverse races within the species. Thus, as noted above, the progeny of the St. Bernard-Great Dane cross are not going to be satisfactory even though each of the parents is homozygous (page 418).

In the human race, it is evident that the peoples of the various nations carry a high degree of hybridization in their gene complex as the result of racial mixtures following migrations to other lands at various times in the past. This is particularly true in a melting pot of the races such as is found in the United States. But even a well-established people, like the English, contains additions to the genotype from the Mediterranean peoples brought in by the Roman invaders. At various times, the Germanic, Norman, French, and other nationalities have added to the racial mixture that is more or less stabilized in the British type of today. Everywhere among the Caucasian peoples, the story is much the same, whether they live in Germany or France or Italy or Spain. Evidence that these established nationalities have developed from marked racial mixtures in the past may be used as an argument for the belief that the final result of the racial mixture in this country will not necessarily be unsatisfactory. It is, in fact, impossible to draw any definite conclusions as to the future, for no one knows what the blending of the diverse genotypes will bring forth in the generations that lie ahead.

In addition to lack of knowledge of the individual human genotypes, the question of mutations is to be considered, because the appearance of some unfavorable character in the progeny may be due to a sudden chromosomal aberration, in one or the other of the parental gametes, that has never been in the germ plasm of either parent previously. The classic example of a mammalian mutation occurring naturally was noted in 1791 when a mutant type of sheep was born to normal parents. The animals belonged to a farmer, Seth Wright, of the Massachusetts colony. This mutation produced a short-legged, or ancon, type of sheep which was highly regarded for a time because it lacked the fence-jumping ability of its long-legged relatives. But the ancon sheep were lacking in other ways and, all things considered, did not measure up to the standards of the normal animals. Accordingly, the mutant type was propagated for some years until the advantages and disadvantages became apparent and better methods of fence building were devised and then was discarded in favor of the generally more desirable long-legged varieties. This particular mutation in the

germ plasm, producing short legs, appeared without warning and was easily propagated because it was dominant over the normal gene complex responsible for length of leg. Most mutations, which have been studied, are found to be recessive in nature, and, therefore, they are unable to alter a particular character unless it is present in the zygote in a homozygous condition. (Fig. 225.)

The upshot of the matter is apparent; it is impossible to determine when the recessive gene for an unfavorable character became established in a particular human gene complex. It may have been during gamete formation in the previous generation, or the recessive gene may

FIG. 225.—Photograph showing the short-legged ancon sheep (left) in comparison with the normal condition (right). (*From photograph by Dr. W. Landauer, University of Connecticut.*)

have been there for untold generations before getting the opportunity to be present in a zygote in a homozygous condition. But it is always true that the chances of an undesirable recessive gene finding a homozygous mate are much greater when the parental chromatin is related than when the gametes have a diverse ancestry. Hence it seems wise to accept the established belief, which in various regions has crystallized into law, that marriage between cousins is not desirable. That is not to say that the progeny of cousin marriages are always below grade. Quite the contrary is the case, as can be seen in examples from various distinguished families. It may be that statistics would show no higher percentage of defectives in the children from cousin marriages than from the union of unrelated persons. Nevertheless, our present-day knowledge of the heredity mechanism makes clear the inherent dangers.

Fortunately the history of a family over a number of generations usually reveals with considerable accuracy the desirability or undesirability of the gene complex even though all the family pedigrees have not been studied with scientific exactness. The extreme examples of an undesirable gene complex with respect to mental characteristics, which after all is the final consideration, are afforded by the studies that have been made of members of the "Jukes" and "Kallikak" families through several generations. Possibly these examples have been held up to view so frequently in the past twenty-five years that they have lost their effectiveness. And perhaps a great deal of the trouble in these families was the result of very unfavorable environmental conditions producing individual modifications. But it would seem that an unprejudiced observer on the side lines would have to conclude that something was wrong with the family genotypes when more than 40 per cent of the individuals in successive generations are mentally defective.

That the genotype is responsible for mental inadequacy and other departures from the normal human pattern is possibly even more strikingly shown by the careful studies that have been made on the behavior of twins with respect to criminal tendencies. It should be emphasized that two types of human twins are recognized, namely, fraternal, or dizygotic, twins; and identical, or monozygotic, twins. Dizygotic twins, as the name indicates, develop from two zygotes; that is, two eggs were fertilized at the same time. Accordingly, except for the fact that they are of the same age, dizygotic twins are no more alike than other members of the family. Monozygotic twins develop from the same zygote and, therefore, have identical genotypes. Such a condition is believed to arise by the separation of the two daughter cells, following the first cleavage of the fertilized egg, and the independent development of the two cells thereafter so that each cell forms a twin. Identical twins are always of the same sex and so nearly alike in appearance that it is usually impossible for strangers to tell them apart.

An examination of the prisons in Bavaria some years ago revealed that one or both members of 30 pairs of twins were imprisoned or had prison records. Very complete information was secured with respect to these individuals. Of the 30 pairs of twins with criminal records, it was found that 17 pairs were fraternal and 13 pairs were identical. Examination of the prison records of the 17 pairs of fraternal twins showed that criminal tendencies in one member of the pair gave no evidence that the other twin would likewise be a burden to society, for it was found that in only two cases had both members of the pair been

imprisoned. Quite the reverse condition was found in the criminality of the 13 pairs of identical twins. The investigation showed that, in 10 cases, both members of the pair had prison records, and in only 3 cases was imprisonment confined to one twin. The numbers of cases used as a basis of these investigations were necessarily small, but the trend is so decisive that it appears safe to conclude that the behavior of an individual as well as his structural pattern is largely the outgrowth of the gene complex received at the time of fertilization.

Eugenics: Negative and Positive

Society has recognized more and more that some individuals are inherently burdened by an undesirable gene complex, though that term may not have been used to express the situation, and accordingly has taken measures to protect future generations against further transmission of the undesirable germ plasm. The traditional method of accomplishing this desirable aim has been through the segregation of the afflicted individuals in government institutions of one kind and another. The trouble with segregation has been, so far, that there are far too many afflicted—with, for example, an estimated 2 to 5 per cent of the population feeble-minded—to make segregation effective. Furthermore, great pressure is continually brought to bear to bring about the release or parole of individuals who are lightly afflicted but, nevertheless, potentially dangerous individuals from the standpoint of heredity. Laws with regard to the requirements for marriage differ widely, with the result that a license denied in one locality can usually be secured in another. Accordingly, many cases are found in which afflicted individuals, who should be permanently segregated, find it possible to marry and produce offspring. And the alarming fact for the future is that the rate of reproduction of mentally deficient couples is probably twice that of couples with high mentality.

Increasingly, the tendency in the United States during the last twenty-five years has been to pass laws requiring or permitting the sterilization of certain classes of defectives of both sexes in such a way that the production of offspring is impossible, though the normal sexual relations of the married state are in no way disturbed. In both sexes, the sterilization operation consists of cutting the ducts from the gonads so that the germ cells cannot pass through them. In the male, the operation is a very simple one, since the testes lie outside the abdominal cavity and the connecting ducts are easily exposed. In the female, an abdominal operation is involved which may fairly be compared in severity with an operation for appendicitis. In 1909, only four states had sterilization laws; in 1934, the number had

increased to 27. These laws have been opposed chiefly on three grounds. It has been argued that sterilization would tend to increase sexual immorality, that it conflicted with the Constitution in that it constituted "cruel and unusual punishment," and that it represented a dangerous infringement of personal liberty. The legality of the sterilization laws of one state, Virginia, was carried to the Supreme Court in 1927 and there upheld, a decision that carried the famous remark of Justice Holmes that "three generations of imbeciles are enough."

The advisability of sterilization is a question that cannot be settled in a few years, but a careful study of the results in California, based on nearly 10,000 legal sterilizations, indicates a much more favorable result than might have been expected. The application of sterilization laws throughout the past ages would undoubtedly have prevented the appearance of many unfortunates, but, at the same time, it is also possible that some of the geniuses of the first rank, who have greatly enriched civilization, would never have been known. The incomprehensibly complex chromatin of the human race can never be analyzed to the extent that all of the possibilities inherent in the offspring of two individuals can be determined previous to their appearance. The offspring of a particular marriage will always be a gamble. But on the other hand, it should be remembered that the principles of selective breeding, which man has rigorously applied in order to obtain desirable domesticated plant and animal types, have been tremendously effective in establishing new varieties far superior to the original stocks. The biologist, knowing that the same hereditary mechanism is at work in the human organism, is certain that the same methods, if it were possible to apply them, would be effective with the heritable qualities in man.

The discussion so far has dealt with the prevention of the transmission of defective chromatin to another generation. To some authorities this is "negative eugenics," which may be helpful to some extent but should be augmented by a policy of "positive eugenics" in which selected human stocks would be encouraged to transmit the desirable genotype to an increasing number of progeny. In other words, every possible measure should be taken to increase the birth rate among the better endowed families rather than to let it continue to sink to lower levels, as appears to be the case at present. Admittedly, if this were possible, much could be accomplished in improving the human race, but just how it could be effected seems to test the limits of human intelligence. Some countries, notably France, have in recent years been experimenting with a general family allowance plan for additional

children, but it will be a long time before any conclusion can be safely drawn as to the desirability of such a plan. It is one thing to adopt a plan that will give an allowance to all families with a large number of children, but quite another to select families that are thought to have a more desirable gene complex and to reward them for increased numbers of progeny, while at the same time restricting other families and requiring them to share in the increased expense of maintaining a subsidy for the selected families.

CHAPTER XVI

THE WEB OF LIFE

In the previous chapters, attention has been primarily centered on the structural and functional features of the human organism. It is now time to broaden this viewpoint somewhat and give attention to man's relationships to other members of the living world, infinite in number, which surround him on every side and with which he is indissolubly linked in a complex living fabric, aptly termed the *web of life.* Man is a part of, not apart from, the living world. His basic requirements for food and clothing are supplied by materials produced by other living organisms. And all plants and animals are necessarily dependent upon the constructive photosynthetic activities of green plants for the formation of the essential foodstuffs carrying abundant supplies of potential energy which may be utilized in maintaining the varied life activities and for the construction and maintenance of protoplasm itself.

In the final analysis, whether or not an organism is successful, as evidenced by its ability to survive and to propagate its kind, depends directly upon its ability to secure adequate food supplies in the particular environment to which it is permanently adapted. The abundance of life and the relative scarcity of suitable energy-supplying, protoplasm-building foodstuffs make it necessary for organisms to compete for their nutritive requirements. The innumerable living organisms surviving today are adapted for every possible environment in which energy-containing substances are to be found. As the English biologist Dendy has well said:

> At the present day we see the surface of the earth teeming with hosts of living things, incalculable in number and of endless diversity in form and structure. Every situation where life is possible is occupied by plants or animals of some kind or other, all specially adapted in bodily organization to the conditions under which they have to maintain their existence. From the bleak and inhospitable summits of high mountain ranges to ocean depths which can be measured in miles, from the perpetually frozen circumpolar regions to the torrid zone on either side of the equator, living things abound. Seas, rivers, lakes, dry land, and air have all alike been taken possession of by representatives of the animal and vegetable kingdoms.[1]

[1] Dendy, "Outlines of Evolutionary Biology," D. Appleton-Century Company, Inc.

Thus it is clear that the world of life, as seen today, presents a bewildering array of species that are able to supply their specific nutritive requirements under very different environmental conditions. Basically, however, all living organisms may be regarded as either autotrophic or heterotrophic in their nutrition. Autotrophic organisms are those which possess the ability to construct, or synthesize, the essential nutritive substances from the abundant inorganic elements and compounds in their environment and are, therefore, independent in their nutrition. Heterotrophic organisms require complex organic

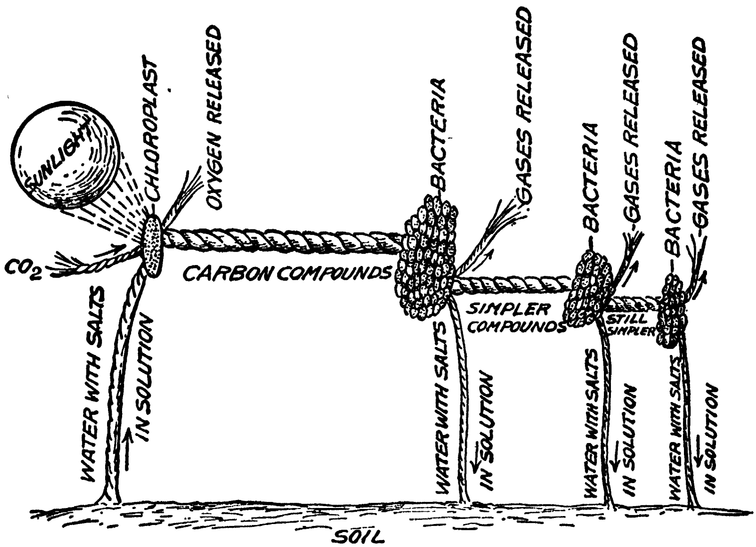


FIG. 226.—Diagram illustrating formation of carbon compounds by photosynthesis in the green plants and their destruction by bacteria and other colorless plants. (*Redrawn from Lutman; slightly modified.*)

compounds as the basis for their food supply and consequently are dependent in their nutrition upon the synthetic activities of the autotrophic forms. It is apparent, therefore, that the autotrophic organisms manufacture food materials for themselves and also for the heterotrophic forms. (Fig. 226.)

AUTOTROPHIC ORGANISMS

Autotrophic organisms consist almost entirely of the green, chlorophyll-bearing plants, equipped for photosynthesis. There is, however, another group of autotrophic plants which though inconspicuous are, nevertheless, of considerable importance, namely, the autotrophic bacteria. These unicellular colorless plants are able to disrupt various highly stable inorganic substances through the action of powerful

intracellular enzymes and to utilize the energy thus released for the synthesis of the complex carbon compounds which are essential for the repair and growth of their protoplasm. Possibly the autotrophic bacteria are to be regarded as the most primitive of all forms of life. Presumably, they were the first type to appear on this earth. The development of chlorophyll and the associated processes of photosynthetic food formation apparently represent later stages of protoplasmic phenomena. The nutritive activities of two important groups of autotrophic bacteria may now be described.

Sulphur Bacteria.—Sulphur is one of the essential elements of living tissues, and it is through the activities of a large and diverse

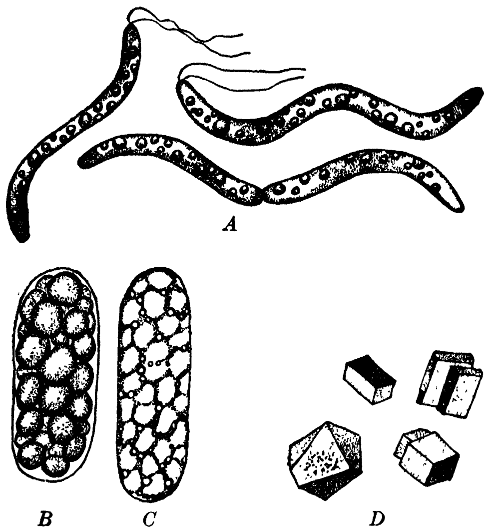


FIG. 227.—Sulphur bacteria. *A*, (*Spirillum granulatum*), with dividing cell; *B*, *C*, *D*, giant sulphur bacterium (*Hillhousia mirabilis*); *B*, normal cell with sulphur bodies filling the entire cell; *C*, an individual in which the sulphur globules have been used in respiration after being kept in tap water for a week; *D*, sulphur crystals obtained when animals are dried. (*Lutman, B, C, D after West and Griffiths.*)

group of sulphur bacteria that suitable compounds of sulphur are supplied for animal and plant nutrition. Thus, in the formation of plant proteins, the green plants utilize the supplies of sulphur obtained from certain soluble sulphates dissolved in the soil waters. The autotrophic sulphur bacteria are able by enzyme action to oxidize the hydrogen sulphide gas (H_2S), released into the air during the decay of organic compounds, to form water and sulphur. In so doing, energy is obtained for the vital activities of the organism. Then the sulphur may be combined with water and oxygen to form sulphuric acid. The latter is released into the soil where it combines with various mineral

elements to form the soluble sulphates, noted above, which are absorbed by the root tissues of the green plants and utilized in protein formation. Sulphur bacteria are unable to survive without an adequate supply of sulphur compounds for their energy requirements. (Fig. 227.)

Nitrifying Bacteria.—The soil-living nitrifying bacteria constitute another important group of autotrophic bacteria that make their living by salvaging the nitrogen in the residues resulting from the decay of plant and animal tissues. There are various species which can be separated into two groups: the nitrite bacteria and the nitrate bacteria. During the decay of proteins, ammonia gas (NH_3) is formed. From the latter, the nitrite bacteria are able to form nitrous acid (HNO_2) by oxidative processes. The nitrate bacteria find the nitrous acid suitable for their metabolic activities and add additional oxygen to form nitric acid (HNO_3). The latter is released into the soil where it combines with mineral elements to form soluble nitrates which are in time absorbed by the green plants and utilized in protein synthesis. (Fig. 226.)

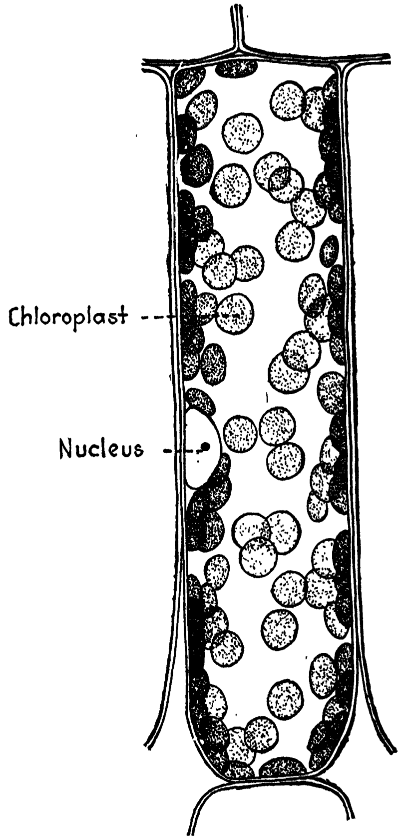


FIG. 228.—Drawing of an active photosynthetic cell (palisade cell) from a leaf. The chloroplasts lie embedded in a thin, transparent layer of cytoplasm (not shown) which also surrounds the nucleus. The center of the typical plant cell is largely occupied by the fluid-filled cell vacuole. (*Sinnott.*)

The Photosynthetic Organisms. It is the presence of chlorophyll in the cells of green plants that is responsible for photosynthesis. Unquestionably, chlorophyll is the most important pigment known to man, for it is essential to the formation of the foodstuffs required by every living organism with the exception of the autotrophic bacteria as just noted. Chlorophyll is also responsible for the liberation of free oxygen into the atmosphere during the photosynthetic processes. Respiration, involving the utilization of oxygen, is essential for every

living cell, for no other method is available to release the potential chemical energy stored in the complex organic molecules. Oxygen is an active element and combines readily with other elements, so that the free oxygen in the atmosphere would quickly disappear were it not for its continuous release during photosynthesis. (Figs. 226, 228.)

The analyses of chlorophyll[1] show it to be a very complex substance in which two chlorophyll compounds are associated. These are known as chlorophyll *a* ($C_{55}H_{72}O_5N_4Mg$) and chlorophyll *b* ($C_{55}H_{70}O_6N_4Mg$). Chemical analyses, however, shed no light on the basic problem, namely, why this particular assemblage of common elements is the only one of all the innumerable compounds known to the chemist able to bring about the photosynthetic reaction. Of particular interest, as previously noted, is the fact that the chemical composition of hemoglobin, the essential oxygen-carrying pigment present in the red blood cells of man and the vertebrates generally, is closely related to that of chlorophyll. Two other yellowish pigments, carotene and xanthophyll, of doubtful function, are associated with chlorophyll.

In the earlier discussion of retinal function, consideration was given to the physical characteristics of the energy-bearing light waves with particular reference to their wave lengths and associated colors in the visible spectrum (page 238). In the utilization of the radiant energy by the green plant cells, the function of absorption of the light rays of the proper wave length is of primary importance. As is well known, an object appears of a certain color because it reflects that particular color of the spectrum and absorbs the other colors. An object that appears black absorbs all the colors of the spectrum and reflects none. The reverse condition obtains with white objects, which absorb none and reflect all the spectral colors equally, thus producing the sensation of white. It is obvious, therefore, that chlorophyll appears green because it reflects the light rays from the green portion of the spectrum and absorbs the rays from the not-green portions, the latter containing the energy-bearing rays essential to the photosynthetic reactions. (Fig. 229.)

The absorption of these rays can be demonstrated by examining the spectrum obtained when the rays of sunlight are passed through a chlorophyll solution. Under such conditions, it will be found that the resulting spectrum is incomplete, for the red and orange rays have been absorbed by the chlorophyll from one end of the spectrum and violet rays from the other. Accordingly, it is evident that the red-orange and the blue-violet rays absorbed by the chlorophyll are the ones that function in photosynthesis. The radiant energy actually

[1] Consult Appendix: Chlorophyll.

used by leaves, under the most favorable condition of photosynthesis, probably never exceeds 3 per cent of the amount available and usually is considerably less than that. Thus the sun continuously supplies an incredible amount of radiant energy, only a very small portion of which is utilized by the green plants for photosynthesis and stored as potential chemical energy in the compounds associated with the plant tissues. Protoplasm has a great capacity to do work so long as it is supplied with the energy-containing foodstuffs. Life is characterized by a

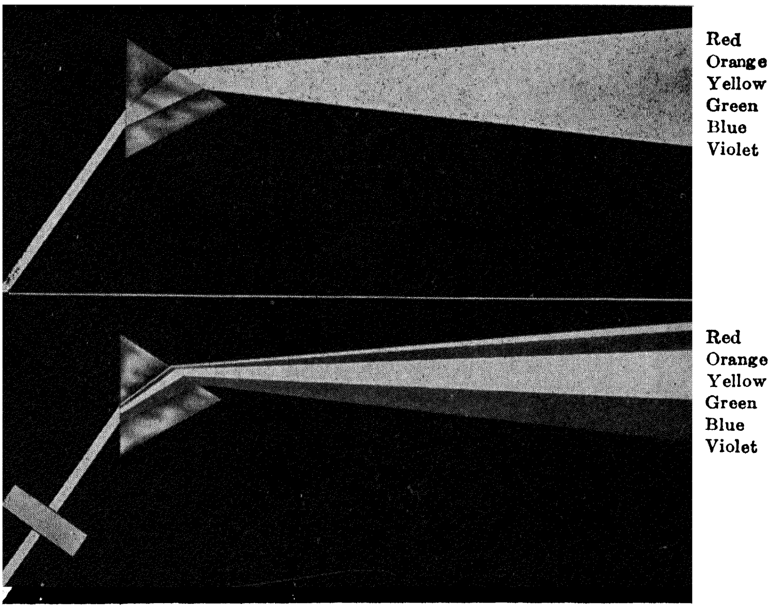


FIG. 229.—Diagram showing the colors produced in the spectrum when a ray of light is passed through the prism of a spectroscope (above); (below) diagram showing the bands absorbed from the spectrum when the ray of light is first passed through chlorophyll solution. Described on page 432. (*Sinnott*).

continuous supply of energy. Living organisms have no method for creating energy but only for the transformation of radiant energy received from the sun. Furthermore, as just stated, the ability to utilize radiant energy is limited to the green plants. They perform this essential function through the synthesis of simple inorganic substances to form complex organic compounds which are suitable for food, and thus available to keep the wheels of life turning.

The physicist defines energy[1] as the capacity to do work and sees that it may be manifested as *energy of position*, shown in gravitation, motion, etc.; as *chemical energy*, which is evidenced in molecular and

[1] Consult Appendix: Energy.

heat phenomena; and as *radiant energy*, illustrated in the phenomen associated with light and electricity. Energy is accumulated a potential energy and later released as active, or kinetic, energy. Th biologist is particularly interested in chemical energy and in the radian energy present in the sun's rays, for the chloroplasts in the green plan cells have discovered the secret of transforming radiant energy int potential chemical energy and storing the latter in complex organi nutritive compounds, the carbohydrates, fats, and proteins; synthese that result from the essential, but poorly understood, process o photosynthesis.

The conventional equation for photosynthesis, namely,

$$6H_2O + 6CO_2 = C_6H_{12}O_6 + 6O_2$$

does not show the energy relations that are basic for the maintenanc of the life functions. Each molecule of glucose that is formed b photosynthesis requires 677.2 calories[1] of radiant energy. Accordingly, the equation for the photosynthetic reaction will read:

$$6H_2O + 6CO_2 + 677.2 \text{ calories} = C_6H_{12}O_6 + 6O_2$$

The oxidation of the carbohydrate molecule in the living tissues durin respiration results in the liberation of this amount of heat energy fo the maintenance of the life functions, as shown in the followin equation:

$$C_6H_{12}O_6 + 6O_2 = 6CO_2 + 6H_2O + 677.2 \text{ calories}$$

Thus, in the living tissues, the potential chemical energy of glucose i transformed into kinetic energy and used to maintain the life activities

But the living organism requires more from the foods that are take in than the mere release of energy—for materials must also be supplie for the repair and growth of the tissues. Our previous consideratio of human nutrition has made it evident that the tissue requirement are supplied in full only when an adequate assortment of proteins i secured from the utilization of various plant and animal tissues (pag 56). In a word, it is recognized that universal food requirement operate throughout the world of life and that the food supply of al organisms rests finally upon the photosynthetic activities of the gree plants. Here, then, is a basic interdependence binding together al living organisms.

Furthermore, the materials accumulated in the tissues of ever living organism, together with the wastes continually formed durin life, must be returned to the great storehouses of nature for late

[1] Small calories: see footnote, p. 86.

reassembling in another cycle of life. This requires the services of the colorless plants, or Fungi, which secure their own nutrition by disintegrating—the processes of decay—the complex organic compounds built up in other organisms, thus making the constituent materials again available. This function of the colorless plants is responsible for the cycle of elements in nature and is just as important as the opposite process involving the constructive activities of the green plants.

HETEROTROPHIC ORGANISMS

Turning our attention to the heterotrophic organisms which are dependent upon the photosynthetic organisms for supplying their nutritive requirements, it may be noted at once that they include the organisms belonging to two widely separated groups, namely, *animals* and *colorless plants* (except for the relatively few types of autotrophic bacteria noted above). It will not be necessary to give further attention to animal nutrition, inasmuch as this subject was fully considered in the earlier chapter on Nutrition, but brief mention of colorless plant nutrition will be helpful. (Fig. 230.)

Representatives of the Fungi are extraordinarily abundant in nature. At the same time, they exhibit wide diversity in their structural patterns and in their nutritive requirements. Throughout, however, there is a common lack of the basic food-synthesizing chlorophyll of the green plants, and hence the colorless plants find it necessary to satisfy their nutritive requirements by utilizing complex foodstuffs as do animals, but, unlike the latter, the Fungi are unable to ingest solid particles of food. Accordingly, it is necessary for the fungal cells to secrete specific extracellular enzymes which digest the solid nutritive substances in their environment, thus liquefying the foods so that they can be absorbed through the unbroken cell membranes. Commonly, the Fungi are termed *decay organisms* because the enzyme actions associated with their nutrition result in the disintegration or decay of the organic materials stored in the dead animal and plant tissues. The compounds thus utilized for the life activities of the Fungi are later returned to the soil and air in a greatly simplified form which permits them to be utilized in the synthetic processes of the green plants—the cycle of elements in nature. In many instances, the Fungi are parasitic, which means, in a word, that to supply their nutritive requirements they invade and destroy the tissues of living plants and animals and cause disease, as will be discussed at length below. In either of the conditions noted above, the essentials of nutrition remain unchanged in that the enzymes secreted by the fungous cells are able to digest the

complex materials whether the latter are present in dead or living organisms. This is termed *saprophytic nutrition.*

The colorless plants adapted for saprophytic nutrition include such apparently diverse types as bacteria, yeasts, molds, mildews, mushrooms, smuts, rusts, and various others, totaling, altogether, many thousands of species. From among these, the common bread mold may be selected for further consideration. It is so widely distributed that usually it is necessary to expose a piece of bread to the air for a

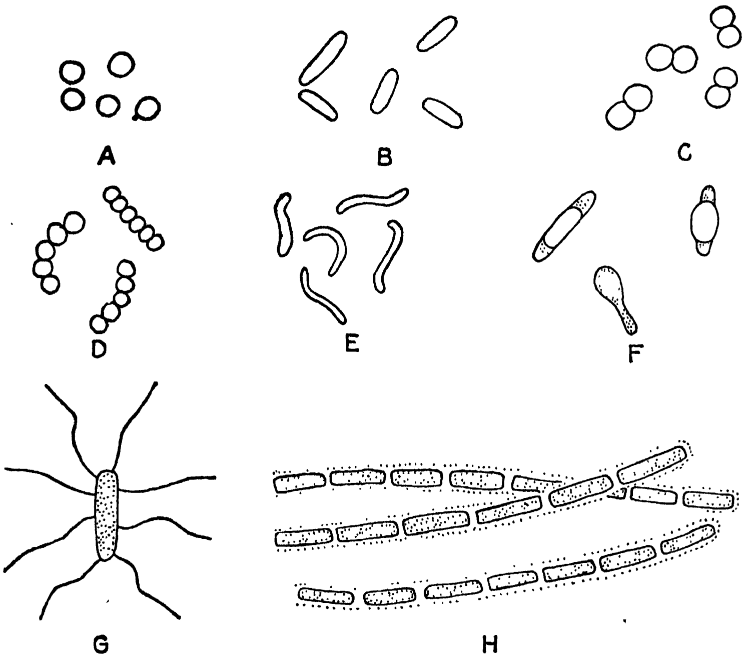


FIG. 230.—Various types of bacteria. *A,B,C,D* are virulent pathogenic (disease-producing) bacteria as follows: *A*, *Staphylococcus; B*, *Myobacterium leprae; C*, *Pneumococcus; D*, *Streptococcus.* *E,G,H* are common nonpathogenic, or saprophytic, forms as follows: *E*, *Spirillum; G*, the colon bacillus (*Bacillus coli*); *H*, the hay bacillus (*Bacillus subtilis*). *F*, three types of spores. Highly magnified. (*Sinnott.*)

few minutes only in order to infect it with the minute, floating spores of the bread mold which are almost invariably present in the dust and air. If sufficient moisture is present, the spores in the bread soon swell, disrupting the cell wall, and then each releases a bit of active protoplasm which immediately begins to permeate the bread substance to secure the essential nutritive materials. In order to obtain the latter, the mold protoplasm secretes digestive enzymes which pass into the bread and digest the solid foodstuffs, thus rendering them soluble. The liquid foods are absorbed by the mold cytoplasm and utilized

for the energy requirements and for the formation of additional protoplasm. (Fig. 149.)

The example just given of the use of extracellular enzymes by the bread mold to secure soluble food materials from suitable solid substances in the environment has wide application in the world of life, and, as a matter of fact, it is exactly what occurs in the holozoic nutrition of man and other animals in the digestion of foods in the alimentary tract. Solid materials taken into the alimentary tract cannot be regarded as being within the body until digestion has taken place and the resulting nutrient liquids have been absorbed by the nutritive epithelium that lines the intestine. To all intents and purposes, therefore, animal digestion is extracellular, and the digestive enzymes are secreted for external use just as are those of the bread mold or other colorless plants.

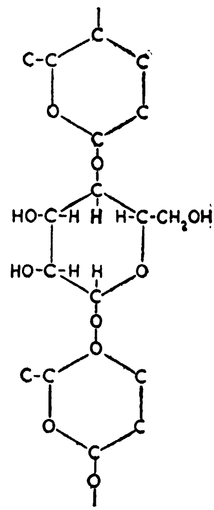


FIG. 231.—Molecular structure of cellulose as determined by x-ray studies. (*Seifriz.*)

ENZYMES

It should be recognized that all types of nutrition exhibited in the living world are directly dependent upon enzyme[1] action. Accordingly, an organism is limited in its selection of foodstuffs by the nutritive enzymes that it is able to synthesize and to employ. The adaptation of an organism, therefore, to a particular environment may be said to rest primarily upon the ability of the nutritive enzymes to digest the available materials. The most powerful enzymes are undoubtedly

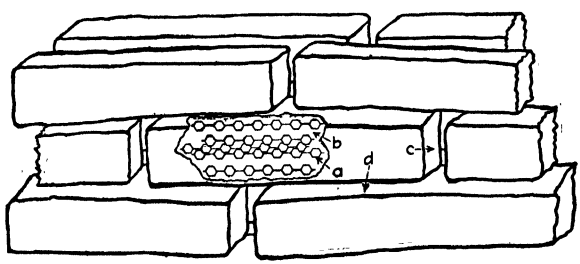


FIG. 232.—Diagram to illustrate possible arrangement of cellulose chains into larger units of cellulose, as in the plant cell wall. *a*, cellulose chain as in Fig. 231; *b,c,d*, position of forces holding larger cellulose units together. (*Seifriz.*)

associated with the life chemistry of the autotrophic bacteria, for, as noted above, these enzymes are able to break down certain very stable

[1] Consult Appendix: Enzymes.

inorganic compounds and make them available to the organisms. Possibly at the opposite end of the scale are the digestive enzymes of the flesh-eating mammals which are limited in their chemical activities to reactions with organic compounds possessing relatively large and unstable molecules. In the chapter on Nutrition, considerable attention was directed toward enzyme actions in digestion (page 63). The earlier discussion may now be broadened somewhat in an endeavor to give brief answers to four questions relative to the enzymes, namely, What are they? How do they work? What do they accomplish? Where do they work? (Figs. 231, 232. Pages 70, 510.)

In the first place, enzymes may be described as nonliving compounds which are formed by the synthetic activities of cell protoplasm. Every cell must be equipped with its battery of enzymes in order to maintain the essential chemical processes associated with the maintenance of the life processes. The chemist recognizes them as catalysts, a group that includes many inorganic compounds and even certain elements. The enzymes associated with chemical reactions in living organisms are much more elaborate in their chemical structure. A catalyst may be defined as any substance that hastens the attainment of equilibrium in a chemical reaction. In so doing, the catalyst itself is not changed.

A well-known example of catalytic action is found in the greatly accelerated reaction between hydrogen and oxygen in the presence of finely divided platinum particles which act as a catalyst. Another catalytic action, and one that can easily be demonstrated, is to be seen in the oxidation of cane sugar. An attempt to ignite a lump of cane sugar with a match will be unsuccessful without the aid of a catalyst which will bring about a chemical reaction between oxygen and the sugar molecules at a comparatively low temperature. An efficient catalyst[1] for this reaction is found in powdered ashes. The test may be made by, first, attempting to ignite the pure sugar by the match flame; the sugar will melt but not burn. If, now, the end of the sugar lump is rubbed in some powdered ashes, it can be ignited and will burn vigorously. The oxidative reaction in the presence of the ash-catalyst will continue until all of the sugar is burned. This shows that the catalyst is not destroyed in the reaction but continues to function in the presence of sugar and oxygen.

The enzymes of living organisms differ from inorganic catalysts, as just described, in being much more complex in their chemical structure. They are colloidal, probably proteinaceous substances. Accordingly,

[1] The author is indebted to Dr. O. W. Richards for calling his attention to this striking example of catalytic action.

the process of adsorption, in which a precipitation of the combining substances on the finely dispersed particles of the colloidal enzyme occurs, appears to be primarily responsible for the acceleration of the chemical reactions. To the chemist, probably the most amazing characteristic of life is the ability to maintain vigorous chemical reactions at comparatively low temperatures. The same reactions in the laboratory, without the catalytic enzyme phenomena, will occur only under a very much higher temperature. Another important characteristic of enzyme activity is its rigid specificity. In general, each enzyme is concerned with a single reaction which takes place in a particular substance or substrate. Thus, in digestion, the enzyme sucrase is required for the splitting of the cane sugar, or sucrose, molecule. In any other substrate than a sucrose solution, this enzyme is an inert substance.

Though a great many enzymes are known, around 100 being available for the various chemical processes associated with the human organism, and though they are, as we have seen, markedly specific in their selection of a substrate, nevertheless, they accomplish their results almost entirely by two processes, namely, hydrolysis and oxidation. By far the greatest number of enzymes are hydrolyzers, which, as indicated by the descriptive term, perform their chemical magic by the use of water molecules, which may be added or removed from a particular compound. Thus, in digestion, as we know, water is added to the complex organic solids (page 62), whereas in the synthetic reactions the opposite condition obtains and water is released (page 66). Or in some enzymes, as in those responsible for intracellular respiration, the reactions are brought about by oxidative processes which result in an increase or decrease in the oxygen present in the substrate.

Enzymes are often divided into two groups on the basis of their ability to synthesize more complex compounds from less complex materials or the opposite condition in which disintegration of the complex substances is incited. Comparatively little is known about the synthesizing enzymes, though every cell must carry its complement of these essential catalytic agents in order to build the protoplasmic materials required for repair and growth. Unquestionably, the amino acids selected from the environment are synthesized by intracellular enzymes to form the exact type of protein required for each cell. Furthermore, the basic process for all life, photosynthesis in the green plant cells, is undoubtedly dependent upon synthesizing enzymes. The presence of one of these enzymes (chlorophyllase) has been definitely established. Blood coagulation, with the formation of the

insoluble protein fibrin, is also seen as the result of synthetic activity incited by a synthesizing enzyme, kinase.

Finally, enzymes may be divided into two groups on the basis of intracellular or intercellular activity. The term *enzyme*, coming from the Greek, literally means "in yeast" and refers to the fact that a substance is present in yeast that is responsible for the chemical activities resulting in alcoholic fermentation. This intracellular enzyme, zymase, can be obtained from the yeast cells when the cell walls are destroyed by grinding. Zymase is only one of many intracellular enzymes that are necessarily present in the cytoplasm of the yeast cells in order for them to synthesize or to disintegrate the various substances essential to the life activities of these cells. Essentially the same thing is true for every type of living cell no matter where found. In addition to the essential intracellular enzymes, heterotrophic organisms, as just noted, must be able to form and to secrete into their environment various extracellular enzymes for the digestive functions so that the available nutritive materials can be absorbed and assimilated by the cells.

As already indicated, the disintegrative enzymes include the digestive enzymes. These have been the subject of a great deal of investigation. Primarily, this is due to the fact that many of the digestive enzymes are formed and secreted in considerable quantities in the vertebrate animals so that they have been relatively easy for the investigator to secure. However, the first digestive enzyme discovered, more than one hundred years ago (1833), was found in plant tissues. It was noted that germinating seeds contained a substance able to change the stored starch grains into sugar. This action was due to the enzyme amylase which is also present in the human digestive tract, where it performs the same function. Some thirty years later, Pasteur discovered that enzyme action was responsible for the formation of alcohol from the sugar molecule and that the enzyme was formed in the cytoplasm of yeast cells. It was not until 1897 that this enzyme, zymase, was extracted from the yeast cells by grinding. It was further shown that zymase, though normally intracellular, was able to incite the same reaction outside the cell. Other important enzymes associated with carbohydrate disruption include sucrase, lactase, and maltase. These, together with lipase, the fat-splitting enzyme, and the battery of important proteolytic enzymes, pepsin, rennin, trypsin, and erepsin, constitute the complement of digestive enzymes associated with digestion in the human organism as discussed in the earlier chapter (pages 63 to 66). Similar enzymes are widely

distributed in every type of organism and apparently are the basis of nutrition throughout the living world.

Brief mention should be made of two other activities of disintegrative enzymes associated with animal respiration and with the so-called deaminization process. The respiratory enzymes are intracellular and are often termed *oxidases* because they disrupt the glucose molecule by the addition of oxygen, as indicated in the equation $C_6H_{12}O_6 + 6O_2 = 6CO_2 + 6H_2O$. Deaminization enzymes are present in the cytoplasm of the liver cells. Acting on the amino acid molecule, when a surplus is absorbed by these cells, they are able to split off the amino acid radical, NH_2, and leave the remainder of the molecule, with the carbon, hydrogen, and oxygen elements to be utilized as a carbohydrate. In this way excess proteins are disposed of. Also, attention was directed previously to the pigment-producing enzyme, tyrosinase (page 400).

Food Chains.—It is hoped that the preceding discussion in this chapter makes it entirely clear that, from the nutritive standpoint, organisms are largely restricted in supplying their essential requirements by the digestive enzymes with which they are equipped. This nutritive adaptation is responsible for the cycle of elements in nature that maintains a continuous supply of the essential elements and, at the same time, binds all organisms together in a nutritive web of life. The latter is woven of innumerable strands, the *food chains*, by which the nutritive requirements of the associated organisms are supplied and to which each particular group of organisms makes a contribution to the nutrition of the other groups possessing different nutritive requirements. The food chains of all animals start from the organic foodstuffs synthesized by the green plants, which, as we know, are capable of supplying the energy requirements and the building materials as well.

A temporary, but very interesting, web of life with many food chains is readily observed in a laboratory hay infusion. The latter is easily started by introducing a few wisps of hay or grass into a battery jar or other suitable receptacle containing tap or pond water. The dried plant tissue contains substances formed by photosynthetic activity suitable for the nutrition of various microscopic organisms, particularly bacteria, which may be present in the water or, in an inactive state, on the hay. The bacteria and other types of fungi, finding the hay infusion environment suitable, quickly become active and start the secretion of enzymes which, in turn, begin the digestion of the nutritive materials of the hay. The soluble compounds thus formed

diffuse through the water, from which they are absorbed and assimilated by the bacterial cells. Such conditions, provided the temperature remains suitable, are highly favorable for bacteria. As a consequence, the bacterial cells reproduce with great rapidity so that, in the course of a few days, untold billions are present in the liquid, and these congregate at the surface of the liquid infusion to form a scum. It is known that under optimum conditions a bacterial cell may divide approximately every half hour.

Marked increase in the numbers of bacterial cells will continue until the stored food materials in the hay, suitable for digestion by the bacterial enzymes, are exhausted or until some larger organism appears in the infusion which finds the bacterial cells suitable for food and begins to prey upon them. Thus, in a hay infusion, it will be found that various types of protozoa, present on the materials at the time the infusion was made, soon become abundant, for they find a very satisfactory food supply in the bacterial cells. Accordingly, the protozoa feed on the bacteria and begin to increase in numbers with amazing rapidity. The first protozoan types to appear in large numbers will usually be very tiny flagellated forms, not much larger than the largest bacterial cells on which they feed. Soon, however, much larger ciliated protozoa appear in increasing numbers, all direct descendants of a few cells present when the infusion was started. And these ciliates get their food by devouring the smaller protozoa and also, to some extent, the bacteria. (Fig. 10.)

Life in this microcosm becomes increasingly abundant for a time until the supply of food stored in the hay begins to be exhausted. When this occurs, as is inevitable unless more hay is added, then the organisms in the food chain rapidly decrease in number. In the course of a few weeks, it will be found that all the active forms of life have disappeared, and the water in the infusion, with no scum at the top, is clear, though inactive spores and cysts await the restoration of adequate nutritive supplies. The energy stored by photosynthesis in the complex compounds has been dissipated, and only comparatively simple substances and elements remain which are resistant to the enzyme action.

But the old infusion contains the inorganic materials that the green plants utilize in photosynthesis. Accordingly, if some suitable green water plants are introduced, and the aquarium is placed in the sunlight, the process of utilizing the radiant energy of sunlight to form the nutritive carbon compounds proceeds at a rapid rate in the presence of the chlorophyll-containing chloroplasts; radiant energy is transformed to potential chemical energy. In time, a body of plant tissues.

suitable for animal or colorless-plant nutrition, will be synthesized. By the introduction of animal life at this stage, there is the possibility of establishing a *balanced aquarium* in which the cycle of elements will be more or less permanently maintained provided the aquarium is kept in sunlight so that the energy dissipated by the maintenance of the life activities of the various organisms will be continually restored.

In a balanced aquarium, the various food chains are woven into a complete pattern—a web of life. Green plant tissues, built up by the photosynthetic actions, may be consumed directly by certain animal types, such as the protozoa, snails, fish, and others. Also, the smaller herbivorous animals are preyed upon by larger carnivorous species, and these, in turn, by the largest types present which represent the climax of a particular food chain. The oxygen released into the water by the photosynthetic activities is utilized by the animals for respiration; the release of waste carbon dioxide by the animal cells is essential to photosynthesis in the plants. The nitrogenous wastes excreted by the animals are immediately attacked by the enzymes of the colorless plants, as are also the plant or animal tissues when an organism dies. In time, the dead tissues are reduced to the inorganic materials suitable for the photosynthetic activities of the green plants. (Fig. 233).

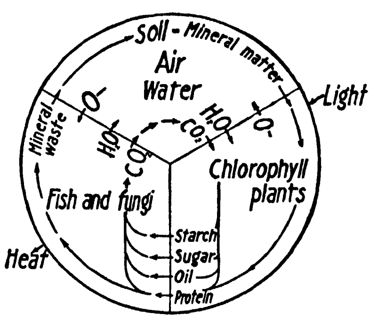


FIG. 233.—Scheme illustrating the cycle of elements in a balanced aquarium. (*Hunter, Walter, and Hunter, "Biology," American Book Company.*)

The cycle of elements and food chains, as just described in a balanced aquarium, are basically no different from those present in typical bodies of fresh and salt water widely distributed over the earth. Representatives of the colorless plants, green plants, and animals are everywhere present; and the nutritive requirements of all the organisms in a particular biotic association, if maintained, are so interlinked as to complete a balanced web of life. These nutritive linkages have been very carefully worked out in many instances by the ecologists, who have as their goal the unraveling of the complex and almost innumerable patterns found in the world of life. And, of course, it is apparent that the organisms in the world in which we live are balanced in essentially the same way as just noted in the individual associations; that so long as the conditions remain adapted for the synthesis of foodstuffs the heterotrophic animal and colorless plant life will be maintained by the autotrophic green plants. (Fig. 234.)

And so in a very real sense one can speak of the aquatic pastures in the fresh and salt waters just as we speak of the pastures present on the soil on which the animals graze. The limnological biologist, concerned with the study of aquatic life in waters, notes that the abundance of life is relatively greater near the surface. Here are found many forms of microscopic floating organisms, both animal and plant, which collectively constitute the plankton, the term meaning "that which is drifted about." The plankton contains many holophytic unicellular plants which constitute the basic source of food for the heterotrophic forms; here as elsewhere photosynthesis is the basis of

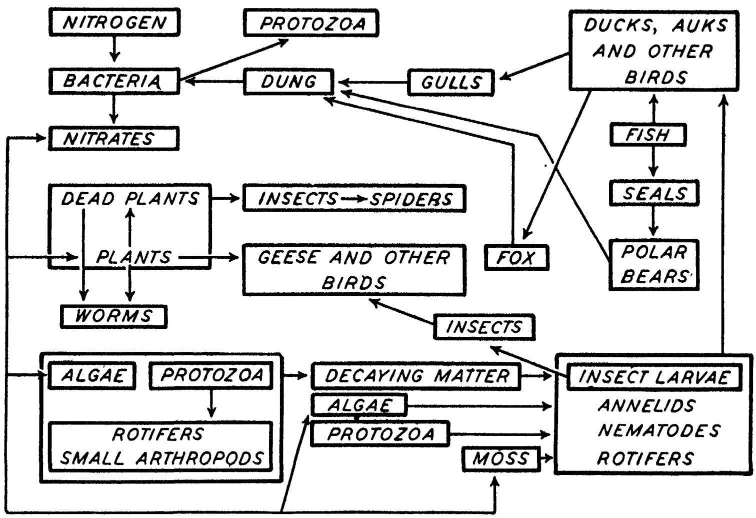


FIG. 234.—Scheme to illustrate the various food chains in the Arctic Bear Island, an isolated community. Arrows indicate the derivation of the food supply by the numerous types of life. (*Buchanan, "Elements of Biology," Harper & Brothers. Adapted from Summerhayes and Elton.*)

nutrition. Though the surface waters may contain a tremendous fauna and flora of organisms in the plankton microcosm, the appearance to the unaided eye is not impressive. But a fine-meshed tow net drawn through the waters will collect an abundance of protistan types, which, under the microscope, will reveal the amazing prodigality of aquatic life. Even so, many of the plankton organisms are so small that they will pass through the finest nets. They can, however, be collected by other methods, such as centrifuging.

The plankton microcosm has its own food chains which bind these microscopic forms in a composite web of life, and the plankton as a whole is, in turn, preyed upon by larger swimming forms which collectively constitute the nekton. The latter consists of active

types ranging in size from large species of Protozoa, barely visible to the naked eye, through a wide variety of Crustacea, to fish of considerable size which represent the climax types. Finally, in large bodies of water with considerable depth, a third association of animals is recognized in the bottom feeders, or benthos forms, which are, so to speak, dependent upon "the crumbs dropped from the rich man's table." At the depths at which the benthos types exist the light rays penetrate but feebly if at all, and, consequently, the environmental conditions are not suitable for the green plants. Therefore, any animals present must receive their food supplies from the abundant life streams in the upper regions. Fish, which are adapted for bottom feeders, typically exhibit marked structural and functional adaptations. Some of the most bizarre types of fish occur in this group. Also in the ocean depths, as in the surface areas, the fungi are well represented, and organic materials, whatever their source, are soon reduced to the inorganic elements and compounds. The latter, eventually reaching the surface waters, pass once more into the stream of life through photosynthetic organisms. Again the cycle of elements is evident.

At the beginning of the chapter, it was stated that the abundance of life upon the earth makes it necessary for all organisms to enter into competition to secure the foodstuffs necessary for their existence. The available food supply is the decisive factor that limits the abundance of life. This fact is particularly apparent in the unicellular forms of life, such as the bacteria and the protozoa. The prodigious abundance of organisms in the microcosm of a hay infusion culture quickly disappear as the food supply dwindles. Woodruff, the famed protozoologist, calculated some years ago that the descendants of a single paramecium, which he cultured in the laboratory for many years, would have formed a mass of protoplasm in a period of 5 years equal to $10^{1,000}$ times the volume of the earth, if it had been possible to provide all the daughter cells with "food and shelter." Even more prolific are the bacteria which, under suitable conditions of food and temperature, will divide every 20 to 30 minutes. It has been calculated that, under these conditions, the descendants of a single bacterial cell have the potentiality of producing more than 280 trillion individuals in 24 hours. At this rate, the descendants would form a mass of bacterial protoplasm as large as the earth every few days. Even large types of animals, such as elephants, which reproduce at a comparatively slow rate will in time overrun the earth if optimum conditions are provided.

And so, with diverse types of living organisms invading every nook and cranny of this earth where adequate food supplies may be secured

and where the environmental conditions permit the maintenance of the living processes, it becomes apparent that the term *life pressure*, which has been used by ecologists to indicate the force directing the organisms into a possible environment, is a very apt one. It will be well at this point to consider the question of environmental relationships, for a close relationship always exists between a particular environment and the organisms subjected to it. Basically, of course, certain fundamental requirements must be supplied by every environment, since they are essential to *life* as we know it. These requirements may be listed as follows: (1) suitable temperature; (2) necessary elements for the growth and repair of protoplasm; (3) suitable conditions for the formation of the carbon compounds, the basic one being carbon dioxide; (4) the presence of a liquid or water environment, the latter being the principal constituent of all living things.

Speaking generally, the earth supplies these basic requirements in abundance. It is always of interest to the biologist to speculate on the possibility of the distribution of these primary life requirements through the unknown spaces of the universe. The opinion of those best fitted to know appears to be quite unanimous that the conditions necessary for the maintenance of life must be very closely restricted and possibly are present only on this tiny pin point of matter, compared with the universe as a whole, which we designate as the earth. The following quotation from the noted British scientist, Sir James Jeans, summarizes the situation as he sees it. He says:

> The physical conditions under which life is possible form only a tiny fraction of the range of physical conditions which prevail in the universe as a whole. The very concept of life implies duration in time; there can be no life where the atoms change their make-up millions of times a second and no pairs of atoms can ever become joined together. It also implies a certain mobility in space, and these two implications restrict life to the small range of physical conditions in which the liquid state is possible. Our survey of the universe has shown how small this range is in comparison with the range of the whole universe. Primeval matter must go on transforming itself into radiation for millions of millions of years to produce an infinitesimal amount of the inert ash on which life can exist. Even then this residue of ash must not be too hot or too cold or life will be impossible. It is difficult to imagine life of any high order except on planets warmed by a sun, and even after a star has lived its life of millions of years, the chance, so far as we can calculate it, is still about a hundred thousand to one against its being a sun surrounded by planets. In every respect—space, time, physical conditions—life is limited to an almost inconceivably small corner of the universe.

The earth not only supplies the basic requirements of the living state in abundance, but, as was pointed out some years ago by L. J.

Henderson in his noteworthy book "The Fitness of the Environment,"[1] there is a maximum fitness in the earth-environment fitness. He has summarized his views on the matter as follows:

> The fitness of the environment results from characteristics which constitute a series of maxima—unique or nearly unique properties of water, carbonic acid, the compounds of carbon, hydrogen, and oxygen and the ocean—so numerous, so varied, so nearly complete among all things which are concerned in the problem that together they form certainly the greatest possible fitness. No other environment consisting of primary constituents made up of other known elements, or lacking water and carbonic acid, could possess a like number of fit characteristics, or in any manner such great fitness to promote complexity, durability, and active metabolism in the organic mechanism which we call life.

THE BIOTIC ENVIRONMENT

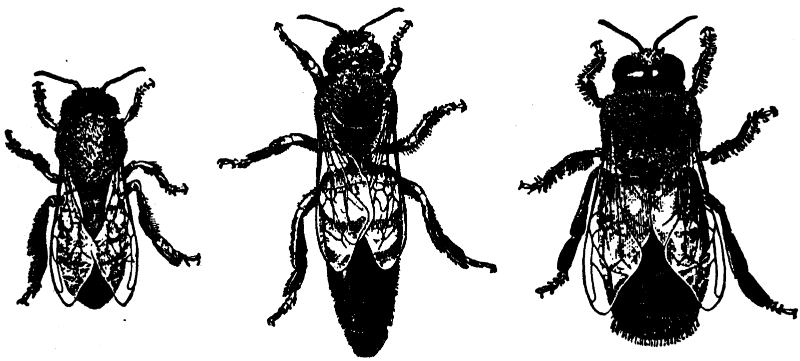
The previous discussion has emphasized the abundance of life and the relative scarcity of food, and we have seen that the latter is a decisive limiting factor which definitely restricts living organisms. It is evident that, in this world of today, a life pressure forces organisms into every possible environment. It must also be emphasized that the environment is not wholly lifeless; there is a living or biotic environment which is possibly of equal importance. Life presses on life! In fact, to a considerable extent, the environment of any organism consists of other living organisms. The same quest for adequate food and shelter that forces them into every possible position in the inorganic world from mountain tops to ocean depths also forces them into all sorts of diversified interrelationships with other living organisms—the biotic environment. The associations thus formed among living organisms may be only transitory and casual, or they may be obligatory and accompanied by marked structural and functional adaptations which make independent survival impossible. For our present consideration, the various biotic associations in the living world may be assembled in four main types, namely, the communal, the commensal, the symbiotic, and the parasitic, which will be considered in the order named.

Communal Associations.—These may be regarded as beneficial groupings of individuals of the same species to form various types of casual and obligatory association. Casual associations are seen in flocks, herds, droves, and even in human communities, all of which are more or less variable. The individuals thus associated are free to come

[1] The Macmillan Company.

and go, while the group as a whole, which has been found helpful, persists. Communal associations also include colonies of various types, composed of individuals that are structurally modified so that membership in the colony is obligatory; an individual so adapted cannot long survive away from the colony. Many striking examples of this condition are to be found in the societies or colonies developed by various of the so-called social insects, such as the wasps, bees, ants, and termites. (Figs. 235, 236.)

Take one of the most common examples of insect colonies, as shown by the honeybee. A colony of bees in a hive consists of three types of individuals which exhibit distinct structural and functional adaptations. There is one fertile female, the queen, on which the life of the colony depends because she is the only one capable of pro-



Worker Queen Drone

FIG. 235.—The honeybee. × 2. (*Wieman, after Phillips. U. S. Dept. Agr., Farmers' Bulletin* 447.)

ducing new individuals. The death of the queen, therefore, means the death of the colony as the older individuals continue to die off. There are several hundred mature males or drones in an active colony, and one of these mates with the young virgin queen during the nuptial flight which takes place following swarming. All of the drones are expelled from the hive at the close of the active season in the fall so that only the queen and workers remain as members of the colony during the inactive season. The workers carry on all the activities of the hive with the exception of reproduction. They are infertile females and never attain sexual maturity. It has long been held that the queen may lay either fertilized or unfertilized eggs. The latter undergo parthenogenetic development, giving rise to the drones, while the fertilized eggs are potentially queens or workers. The development of queen or worker appears to be determined by the food supplied to the female larvae during early stages by the nurse-workers,

but there is also the possibility that hormonal secretion may be involved.

Young queens are desired only when the colony becomes so large that the hive is crowded. Under this condition, workers construct a special queen cell, in which the queen lays a fertilized egg. The attainment of sexual maturity by the young virgin queen is the signal for swarming. The main feature of this phenomenon is the departure of the old queen from the parental hive, accompanied by some thousands of workers who remain her loyal subjects. The swarm seeks a

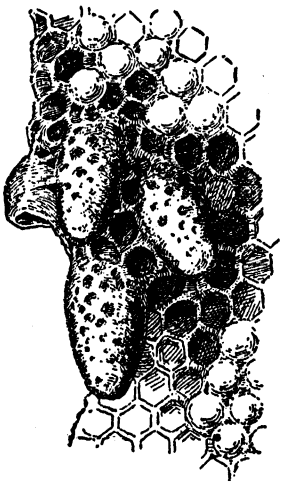


Fig. 236.

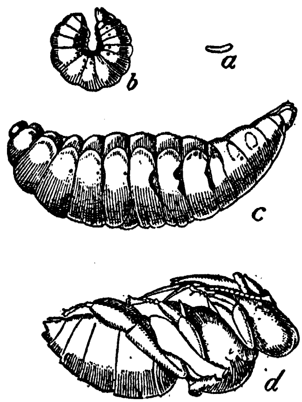


Fig. 237.

Fig. 236.—Various types of cells in the comb of the honeybee. Three large queen cells, numerous honey cells (capped), and worker brood cells (uncapped) are shown. (*Wieman, after Phillips. U. S. Dept. Agr., Farmers' Bulletin* 447.)

Fig. 237.—Development of the honeybee. *a*, egg; *b*, young larva; *c*, old larva just before pupation; *d*, pupa. × 3. (*Wieman, after Phillips. U. S. Dept. Agr., Farmers' Bulletin* 447.)

new hive; and when a suitable one is found, normal routines are once more established. And now the virgin queen leaves the old hive on her nuptial flight, accompanied by the drones. Mating occurs with one of the drones during the flight, and then the young queen returns to the parental hive and begins her reign over the less adventurous workers who remained behind when swarming took place. (Fig. 237.)

The duties of the workers are almost legion in number, since they are responsible for the maintenance of the hive, supplying food, nursing the larvae, and protecting the interests of the colony in every way. The life of the colony depends upon the collection of various substances from flowering plants. Among these is nectar, a scented liquid rich in sugar which, slightly modified by the evaporation of some of the water,

is stored as honey in the cells of the wax honeycomb. Abundant collections are also made of pollen. This activity is essential to bees and plants alike. Since pollen, or bee bread, is rich in nitrogenous substances which are not present in honey, it is an essential bee food. For the flowers, pollen is an essential element in sexual reproduction as it contains the male nuclei. The distribution of pollen from flower to flower, by bees and other insects, is required for cross-fertilization. An important and interesting commensal association exhibited between insects and flowering plants is considered below (page 452). Finally, the workers collect resinous secretions of various plants which,

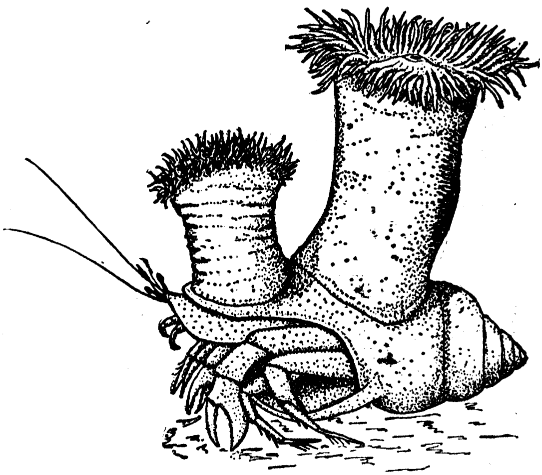


FIG. 238.—Example of commensalism existing between hermit crab and sea anemones. Frequently, the anemones completely cover the mollusc shell which the crab has appropriated. (*Wieman.*)

as bee glue, or propolis, are used to cover the interior on the hive and to fill the cracks, much as paint and putty.

Commensal Associations.—In the present discussion, this large group of associations will be restricted to external partnerships between individuals of diverse species, which are of mutual benefit. The symbiotic associations considered below have the same general basis but are essentially more intimate, since the association is internal rather than external. Commensalism may be obligatory but frequently appears to be purely casual and accidental in nature. A classic example of this condition is seen in the well-known partnership frequently found between hermit crabs and sea anemones. The latter attach themselves to the mollusk shell which the hermit crab has appropriated as a trailer home and are carried from place to place as the crab searches for his daily food supply. Crumbs from the latter are noteworthy

additions to the diet of the anemones. The advantages of this arrangement appear to be all with the anemones, and possibly this is the condition, but the general belief is that the batteries of stinging cells borne by the anemones serve as highly desirable arsenals for the defense of the hermit crab. The crabs and anemones survive in the absence of

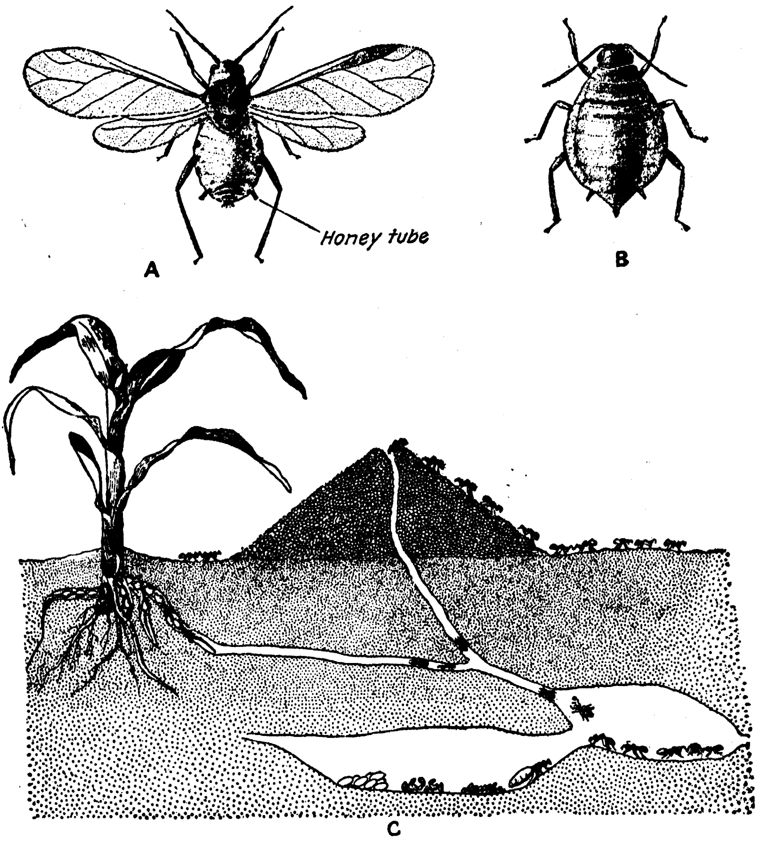


FIG. 239.—The corn-root aphid (*Anuraphis*). *A*, winged form; *B*, wingless form; both enlarged. *C*, diagram illustrating the care of the adults, underground, by the ants during winter. In the spring the aphids are placed on the young corn plants. (*Wolcott, after Davis. U. S. Dept. Agr., Farmers' Bulletin* 891.)

their casual commensalism, but probably they are more successful in life's battles when they are associated. (Fig. 238.)

Another frequently cited example of commensalism is found in the relations existing between certain species of ants and the plant lice, or aphids. The latter secure their nourishment by piercing young plant tissues with their specialized mouth parts and sucking up the cellular juices. The aphids convert much of the ingested food into a

nutritious "honeydew," which the ants find highly desirable for their nutrition. Accordingly the ants endeavor to maintain herds of the aphid "ant-cows," thus applying the same principle that man does with his herds of milk cows. In some instances, as in the corn-root aphis, the ants maintain the aphids in their own colonies during the winter. In the fall, the aphids lay eggs in the galleries of the ant colonies, which hatch in the spring. The young aphids are carefully nurtured by the ants and, at the proper time, are placed on the corn roots. Here the aphids begin to feed and to produce the honeydew for their owners. The ants lick the honeydew from the leaves, where it was secreted by the aphids, or they may "milk" the aphids by stroking them with their antennae and thus secure the droplets of liquid food just as they are released. (Fig. 239.)

Some of the most interesting commensal relationships have been established between insects and flowering plants. These provide the insects with an abundant food supply of pollen, which is very rich in protein, and, at the same time, as noted above with the honeybee, insure cross-fertilization for the plants by means of the pollen grains containing the male nuclei, which the insects carry from flower to flower. Insects are often attracted to the flowers by the scented nectars that also serve as food. Nectar, slightly modified, is stored as honey and is a highly nutritious energy food. The commensal relationships between insects and flowers may be purely casual, as seen in the honeybee which collects nectar and scatters pollen from a wide variety of flowers. Or the insect-flower relationship may be obligatory, as shown for example, in the yucca plant and the Pronuba moth, where it is associated with an almost unbelievable degree of specialization. (Fig. 240.)

There are several species of liliaceous plants belonging to the genus Yucca, each of which is dependent for fertilization upon the females of a particular species of Pronuba. The pronuban females, unlike any other moth, are provided with prehensile mouth parts adapted for grasping and also with a peculiar egg-laying apparatus, or ovipositor, which may be used to penetrate the delicate plant tissues of the yucca flower. Even more remarkable than the structural adaptations of this amazing insect are the instincts directed toward insuring the fertilization of the plant in order to produce seeds, a certain portion of which are used as food by the larval insects. The yucca blossoms are open at night. The night-flying female moth enters a flower soon after dark and begins to collect the pollen grains from the stamens. The sticky pollen grains are carefully formed into tiny pellets. When sufficient pollen has been collected, she forms a hole with the ovipositor

in the pistil of the flower in which the seeds are produced and lays one or more eggs in close proximity to the embryonic seeds. The production of seeds with the stored food depends, of course, upon pollination. Accordingly, the female moth, having laid the eggs, next insures seed development by inserting the previously collected pollen balls in the

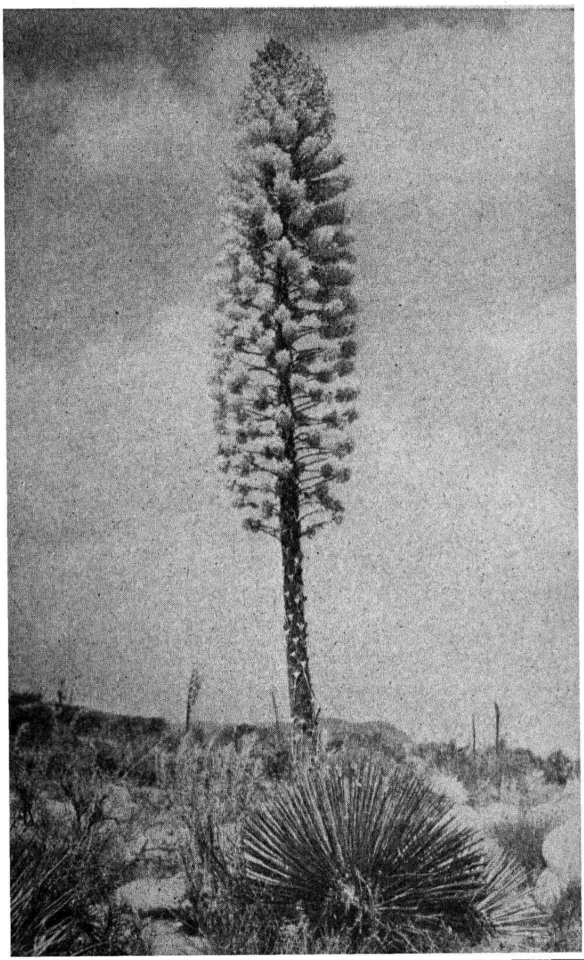


Fig. 240.—Photograph of the Yucca in flower. The plant may reach about 18 ft. in height. Southern California. (*Haupt.*)

tip, or style, of the pistil. Here the pollen grains germinate, and the male nuclei later unite in fertilization with the female nuclei of the embryonic seeds. The seeds, with a large amount of food available for the insect larvae, soon develop. It is important to note that the female moth lays only a few eggs in the pistil of any one flower so that

the larva do not require all of the seeds for their nutrition, the remainder being available for the propagation of the plant.

Symbiotic Associations.—The term *symbiosis*, which literally means "living together," will be restricted in the present discussion to mutually beneficial internal partnerships between diverse species. Thus, as a rule, the symbiotic associations are much more intimate in nature than in the commensalism noted above. Some of the best

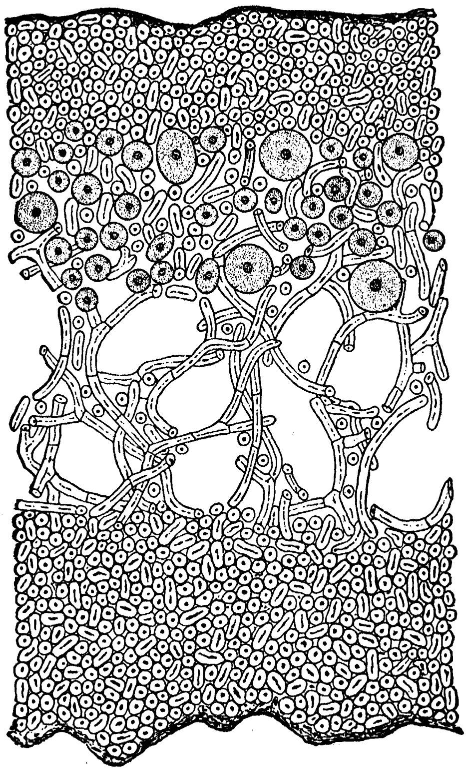


FIG. 241.—Drawing illustrating vertical section through the tissues of a lichen (*Physcia*). The green alga cells (stippled) are seen to be surrounded by interlacing fungus filaments; the latter form the main body of the lichen. × 500. (*Haupt.*)

examples of the symbiotic conditions are found in the plant world. Among these, the classic example of a symbiotic plant, the lichen, may be selected for consideration. Microscopic examination of the lichen plant body shows that it consists of a filamentous fungous plant living in close association with a unicellular green alga. The intertwining fungal filaments form the mass of the body of the lichen but with numerous green alga cells interspersed. And so, the lichen is a "double plant," since it consists of two distinct plant types living together and

forming a composite organism in which each retains its identity. It is generally held that this association between fungus and lichen is of mutual benefit. Possibly, however, the partnership is not on an equal basis, for the continued life of the fungus is entirely dependent upon the photosynthetic activities of the alga, whereas the latter can survive independently. At all events, the lichens are a very successful type of plant organism for they can survive in exposed surfaces, as on rocks, where no other plant life is possible. Accordingly, they are the pioneers in the colonization of a new region and pave the way for the later immigration of the more highly developed types of plants as soil conditions become suitable. (Fig. 241.)

Another important symbiotic plant association is found in the Mycorrhiza, or root-fungi, which have developed a symbiotic relationship with various important trees, such as the oaks and beeches. The growth of the root fungi forms a felt-like covering over the root tissues from which they receive nutritive materials. At the same time, they make various essential salts from the soil available to the host tree. Another important symbiotic relationship between green and colorless plants occurs in the roots of the so-called leguminous plants, such as the pea, bean, alfalfa, and clover, which harbor certain bacteria, the symbiotic nitrifiers. These nitrogen-fixing bacteria live in great numbers in special root tubercles where they are protected and nourished by nutritive materials from the host tissues. The importance of the nitrogen-fixing bacteria to the green plants and to man lies in the fact that they are able to synthesize soluble nitrogenous compounds from the inert nitrogen of the air. These nitrogenous compounds are utilized in the synthesis of plant proteins which are available for animal food or for the enrichment of the soil if the leguminous plants are allowed to remain and decay later takes place. (Fig. 242.)

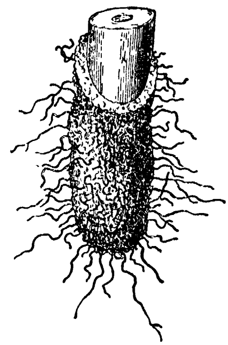


FIG. 242.—Root tip of beech covered with the micorrhiza filaments. (*Woodruff, after Pfeffer.*)

But symbiotic associations are by no means restricted to the plant world; they exist between plants and animals and also between various species of animals. One of the most common examples of a symbiotic plant-animal relationship is to be noted in the ubiquitous green hydra. The green color of hydra is due to the presence of a holophytic symbiont, the unicellular alga Chlorella, which occurs in great numbers. Now, the interesting fact is that these tiny plant cells, though actually living within the body walls of the hydra, are not injurious. On the

contrary, it is clear that the association between plant and animal is of mutual benefit, for the metabolic wastes of the hydra cells are needed by the plant for photosynthesis. On the other hand, the excess oxygen liberated by the Chlorella cells during photosynthesis is utilized by the hydra cells in respiration. The photosynthetic activities of the alga cells necessarily cease when the animals are placed in the dark. Such hydra soon lose their green color and, though they are able to survive if food is available, do not show so great vitality as those kept in light in which the symbiotic condition is maintained. (Fig. 147.)

Parasitic Associations.—A parasite may be defined as an organism that lives at the expense of another organism, the host. Thus the host-parasite relationship is not one of mutual advantage, as exemplified in the various types of biological associations previously noted, but the balance turns toward the parasite. No sharp line of division can be drawn between symbiosis and parasitism but rather a gradual shading from a mutually beneficial condition to one that is slightly parasitic, with the series ending finally in a parasitic association in which the parasite contributes nothing to the host and takes all. Parasitic organisms may be divided into two groups: external parasites (ectoparasites) and internal parasites (endoparasites). In general, an ectoparasite exhibits relatively slight adaptation for the parasitic relationships, and the association with a particular host species is more or less casual and transitory. Thus such external parasites of man as the mosquito, flea, or louse find it possible, when the occasion demands, to supply their nutritive requirements from various other host species. Or the destructive insect pests of trees may prefer a certain species; failing that, they will find the plant tissues of other species hardly less suitable.

Contrariwise, the typical endoparasite shows marked structural and functional adaptations which make it necessary for it to inhabit the internal tissues of a particular host species. Thus the endoparasite is usually an obligate parasite, since survival is not possible except in one host species. Furthermore, many of the obligatory endoparasites have complicated life histories which may involve obligatory habitation in a certain host species at one time and in one or more separate species at another period in the life cycle. Typically, the type of reproduction in the parasite varies from sexual to asexual or vice versa when the parasite passes to the new host. In the malaria parasite, for example, the reproduction is entirely asexual in man; but in the body of the mosquito, sexual reproduction is encountered. In general, the structural changes associated with parasitism are markedly degenerative in nature. This condition is particularly evident in the

nutritive and sensory organs of the parasite, which are essentially without function since those of the host supply both. On the other hand, there is usually a tremendous elaboration of the reproductive

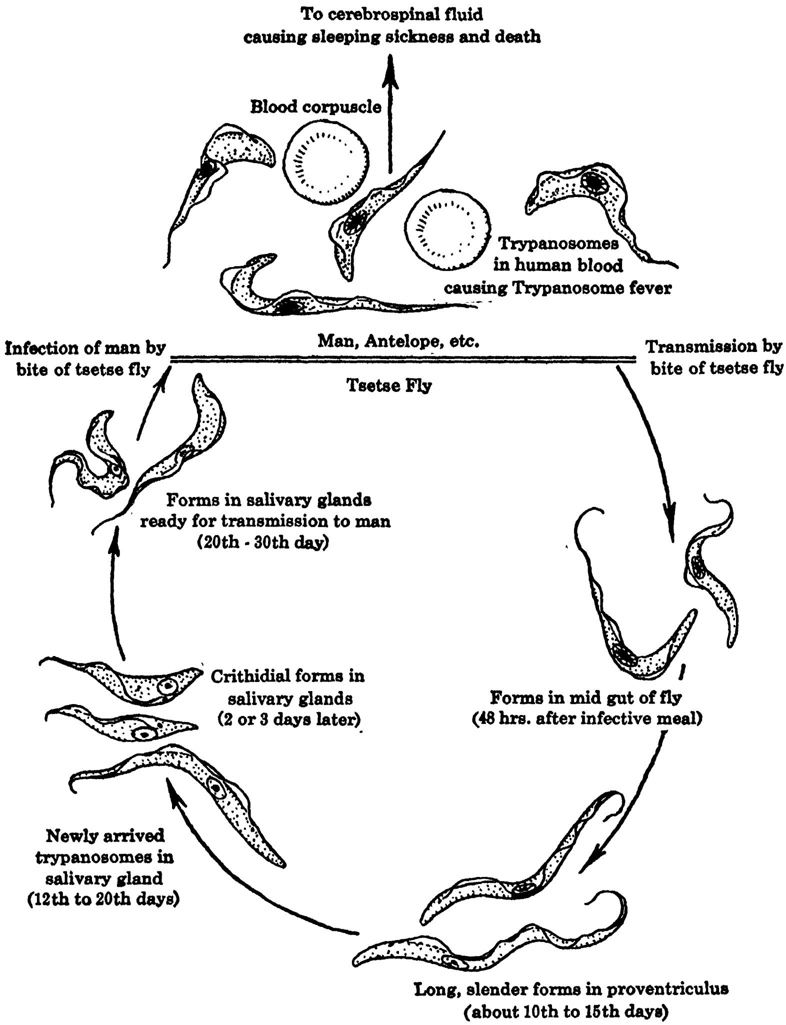


FIG. 243.—Diagram illustrating the life history of *Trypanosoma gambiense*, responsible for African sleeping sickness. (*Chandler, "Animal Parasites in Human Disease," John Wiley & Sons, Inc.*)

mechanism so that the highly specialized endoparasite is little more than a mechanism for the production of germ cells.

Wide variation is also found in the so-called host-parasitic relationship, primarily with reference to the host tolerance. It is evident

to the parasitologist that a correlation exists between the degree of tolerance and the length of time that the association between a particular host species and the parasite species has persisted. In host-parasite relationships of long standing, tolerance of the parasite by the host seems to have developed. Under the conditions, the parasites secure a good living from the host, but their numbers do not become so great that they destroy vital organs and thus kill the host and make it necessary to secure a new home. A well-known example of this condition is seen in the relations existing between certain blood-dwelling protozoa, the trypanosomes, which are the causative agents of African sleeping sickness, and the domesticated animals in the affected regions. The latter harbor considerable numbers of these parasites in their blood, but the host-parasite relationship is such that the parasitic infection is in some way kept down to a point where fatal injury is not sustained by the host. Individuals of the same host species brought into this region from areas outside the sleeping-sickness zone will quickly become parasitized with the blood-dwelling trypanosomes. But, under these circumstances, the parasites increase with great rapidity in the foreign hosts and soon kill them. In general, then, it seems probable that the death of a host by parasitic invasion indicates a relatively new host-parasite relationship. (Fig. 243.)

It may be opportune at this point to indicate certain distinctions between a parasitic organism and a predator. A predator is an animal that preys upon and speedily kills individuals of the same or other types, which are suitable for food, as in the case of the flesh-eating, or carnivorous, animals. When the predator again becomes hungry, it repeats the process. The true predator is therefore different in its behavior from that of the true parasite which, as just noted, is best served when the host is long-lived.

Parasitism is very widespread in the living world. Exact data are not easily obtained, but a conservative estimate would probably show that at least 50 per cent of the plant and animal species supply all or part of their nutritive requirements by parasitizing other species. In the plant kingdom, as would naturally be expected, most of the parasites are found among the colorless plants, which, as has been shown earlier, are dependent upon the organic foodstuffs for their nutrition just as are animals, and they secure the latter from dead tissues of animals and plants, or, in the many parasitic species, from the tissues of living organisms. In either instance, the essentials of the nutritive activities are unchanged; that is, Fungi, whether saprophytic or parasitic, supply their nutritive requirements by subjecting complex substances to extracellular digestion, as described above for

bread mold. From the standpoint of animal parasitism, the unicellular fungi, in particular, the bacteria, are of the greatest importance. The major diseases that affect mankind are for the most part due to bacterial invasions of various tissues and organs of the body. Among these are such important diseases as typhoid, tuberculosis, diphtheria, anthrax, various virulent streptococci infections, and a host of others. Hardly less important to man are numerous other fungal parasites that produce disease and destruction among domesticated animals or in important domesticated plant types such, for example, as the wheat rust, chestnut blight, white pine blister, and the comparatively recent Dutch elm disease. (Fig. 244.)

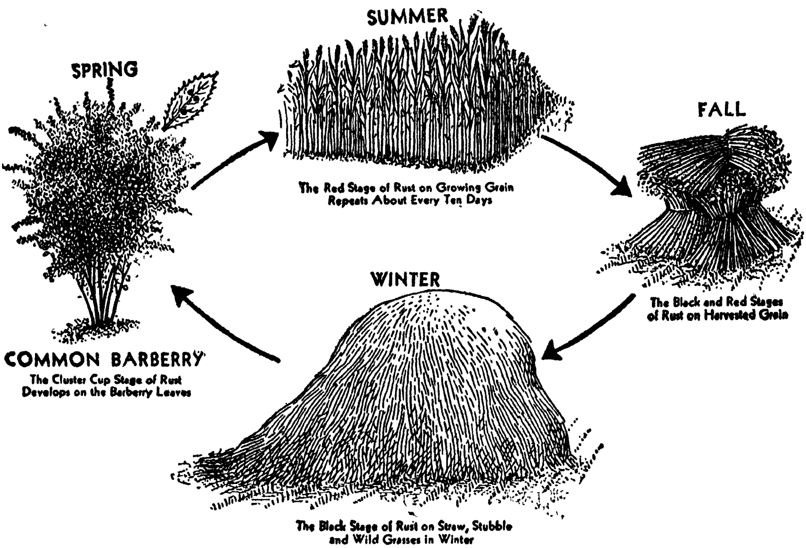


FIG. 244.—Diagrams illustrating the life history of the wheat rust, an important parasite. (*E. T. Smith, "Exploring Biology," After U. S. Dept. Agr.*)

Though much less common, parasitism is also in evidence among the chlorophyll-bearing plants. This is very interesting because, when it occurs, the amount of chlorophyll is correspondingly reduced. Three well-known examples, as seen in the mistletoe, dodder, and rafflesia, will be sufficient to emphasize the relationship between parasitism and chlorophyll and the changes associated with parasitism.

The mistletoe, which has found such favor at the holiday season, is partially parasitic. It fastens itself upon the host tree and develops highly specialized peg-like roots, the haustoria, which push through the outer bark and into the underlying vascular tissues. Through the haustoria, the mistletoe secures essential supplies of water and dissolved salts from the host and builds these up into food materials by

its own photosynthetic apparatus. It is, then, parasitic in that the raw materials necessary for nutrition are taken from the host. A rather common weed, the dodder, exhibits a greater degree of parasitism in the adult stage when it becomes entirely dependent upon the host plant for the essential foodstuffs. In the early stages of development, the dodder is an independent plant growing in the soil, with chlorophyll and active photosynthesis. Increasingly, however, as the plant matures, the chlorophyll disappears, and the dodder, twining around a host plant, develops haustoria which invade the host tissues. In time, the plants completely lose connection with the soil and become entirely parasitic upon the host plant. (Figs. 245, 246.)

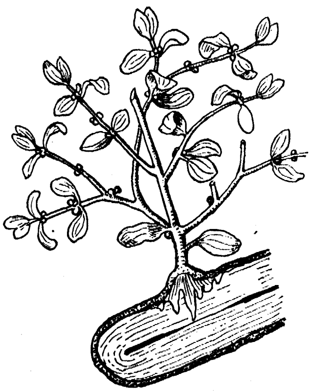


FIG. 245.—Mistletoe, a parasite on various deciduous trees.

Parasitism among the higher plants probably reaches a climax in the tropical plant, *Rafflesia arnoldii*, which is closely restricted in its distribution to Sumatra. The degenerative changes, typically associated with the endoparasitic condition, are nowhere more strikingly illustrated than in this parasitic spermatophyte. It has entirely lost the chlorophyll-bearing tissues, and, in addition, the characteristic plant body, with root, stems, and leaves, has been transformed into a mass of colorless filaments. These lie under the bark of the host tree, ramify through the host tissues, and continuously rob them of a portion of their nutritive materials. Thus rafflesia is entirely dependent upon the host. But the reproductive organs have become greatly enlarged, and this parasite develops the largest known flowers, measuring as much as 3 ft. in diameter and

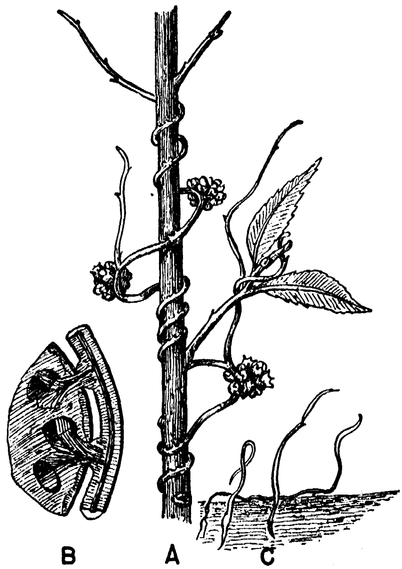
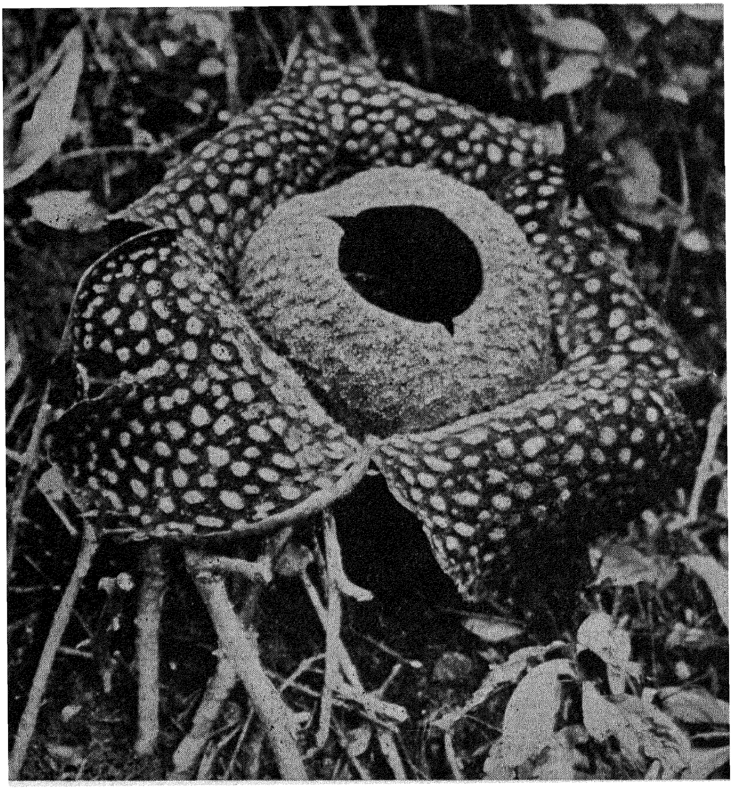


FIG. 246.—The dodder. *C*, young seedlings; *A*, mature parasite twining around the host plant; *B*, microscopic section of the host tissues with dodder tissue attached by haustoria. (*After Strasberger. Redrawn by L. Krause.*)

weighing some 25 lb. There are no external indications of the presence of rafflesia in the host plant until the parasite blooms and the enormous blossom breaks through the bark. Fertilization and seed formation can thus be effected. It is clear that rafflesia exhibits a complete adaptation to the parasitic life. (Fig. 247.)

In the Animal kingdom, as a whole, parasitism is widely distributed and apparently more common than in plants. Parasitic species are



Ewing Galloway

FIG. 247.—The enormous flower of Rafflesia, the parasitic seed plant.

known to occur in every animal phylum with the exception of two: the Porifera (sponges) and the Echinodermata (starfish, sea urchins, etc.). However, from the standpoint of parasitism, the four most important phyla are the Protozoa, Platyhelminthes, Nemathelminthes, and Arthropoda, all containing numerous important parasitic species which infect man and important domesticated animals and produce many virulent and infective diseases. The description of parasitism in aberrant plant types, as given in the preceding paragraphs, strongly

emphasizes the degenerative changes that accompany increasing adaptation to parasitism, with the fully adapted parasite existing solely for its reproductive activities and bleeding the host white to secure nutritive materials for conversion into the reproductive elements of the parasite.

The varities of animal parasites are legion in number, with every conceivable modification of body plan. It will be possible to indicate only three or four common examples which will, perhaps, give some inkling of the condition associated with animal parasitism. In the first place, the body tissues of parasites, whether in a plant or in an animal, are admirably suited for absorbing the nutritive materials of the host. This condition is well exemplified in tapeworms, which are commonly found as intestinal parasites in man and other vertebrates. The body of the tapeworm is long, flattened, cylindrical—some species reaching a length of several feet. It consists of a large number of segmental structures, the proglottids, which contain the reproductive mechanism. The mature proglottids are continually detached from the posterior end of the animal when they are mature, and the reproductive elements are ready to function. Anteriorly, the tapeworm ends in the scolex, a unique structure about the size of a pinhead, which is embedded in the wall of the alimentary canal of the host. Having once gained attachment to the alimentary canal of the host, the parasite floats idly in the nutritive stream supplied by the host and absorbs such nutritive materials as are necessary to maintain the operations of the reproductive mechanism at full speed! (Fig. 248.)

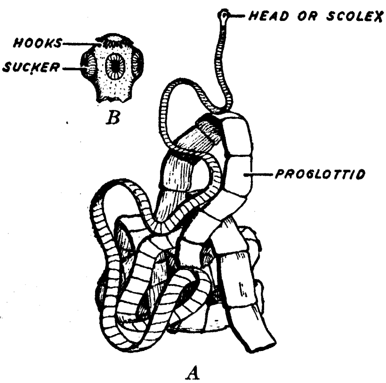


Fig. 248.—Diagram illustrating structure of the tapeworm, *A*; *B*, head enlarged. (*Buchanan, "Elements of Biology," Harper & Brothers.*)

Even more striking are the degenerative changes found in the amazing parasite, Sacculina, which infects the crab, Carcinus. This situation is all the more impressive because Sacculina, which is itself a crustacean closely related to the barnacles, hatches from the egg as an active free-swimming individual, giving no indications that it is soon to become a degenerate internal parasite. But, nevertheless, after a short period of independent existence, Sacculina attaches itself to some membranous structure on the body of the crab and then the degenerative changes begin. These continue until the body and legs disappear, and only the head, denuded of all sense organs and other

external structures, remains as a tiny sac-like body. In this condition, entrance is made through the membranous tissues of the body wall, and Sacculina becomes an internal parasite. From the point of entrance, wherever that may be, the parasite gradually works its way among the tissues until it reaches the abdominal region of the crab. Here it begins to grow and produces innumerable fine filamentous branches which extend to all regions of the body by way of the blood channels and continually absorb nourishment from the blood for the formation of reproductive cells. (Fig. 249.)

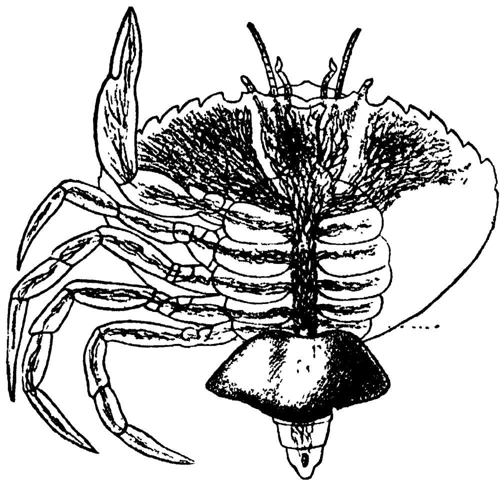


FIG. 249.—Diagrammatic drawing of a crab parasitized by another crustacean, Sacculina. The latter produces filamentous structures which ramify throughout the tissues of the body of the crab. Note the large brood sac. *Cf.* page 462. Appendages shown on one side. (*Lane, "Animal Biology," P. Blakiston's, Son & Company, Inc.*)

In preparing for reproduction, Sacculina in time develops an external, tumor-like brood sac on the ventral surface of the abdomen. First, the tissues of the body wall of the crab are dissolved in a small area, through which the developing *brood sac* protrudes, gradually forming a large brownish-colored oval-shaped body in which the male and female gametes are formed. After fertilization and early development, the embryos are released in the free-swimming stage with which the description began. Earlier zoologists, unaware of the life history of Sacculina and having no conception of the origin of the brood sac, regarded the parasitized crabs as a distinct species.

However, even though Sacculina undergoes this incredible transformation, its life cycle is not complicated by obligatory association with a second host as is the condition in many parasites. Possibly the two best known examples of parasites with more than one host are

the malaria parasite and the liver fluke, each of which may now be briefly considered.

The malaria parasite, *Plasmodium vivax*,[1] belongs to the Protozoa and is of microscopic size. Great numbers of the parasitic cells may be introduced into the blood stream of man by the attacks of infected mosquitoes. In man, the parasite finds the blood stream a suitable habitat and lives as an intracellular parasite of the red cells where it grows and reproduces asexually, finally destroying the host cell as the

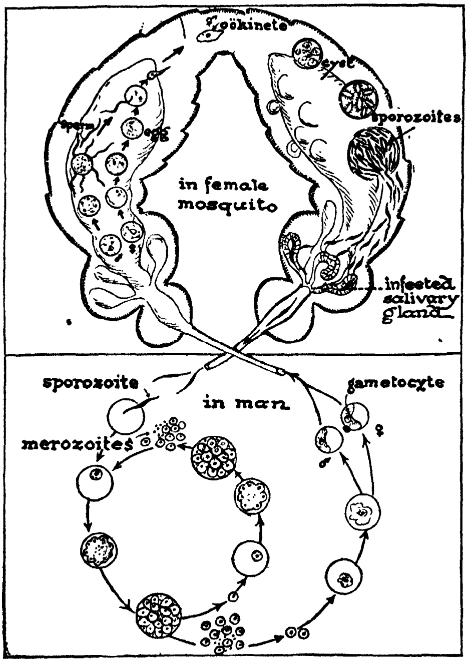


FIG. 250.—Diagram illustrating the life cycle of the malaria parasite; in man (below) and in the female mosquito (above). (*Hunter, Walter, and Hunter,* "*Biology,*" *American Book Company.*)

newly formed parasites are liberated into the blood stream. New red cells are entered, and the cycle of asexual reproduction and cell destruction is repeated, possibly many times. If the patient suffering from malaria is again bitten by a mosquito, some of the infected red cells may be obtained by the mosquito. If so, these cells will undergo sexual reproduction in the walls of the alimentary tract of the mosquito. In time, the zygotes thus formed divide repeatedly, and each quickly produces great quantities of active cells that finally assemble near the salivary glands. They may then be introduced into the human blood stream again at the first opportunity as originally. Thus

[1] Consult Appendix: Plasmodium.

the malaria parasite has two obligatory hosts: a vertebrate in which asexual reproduction occurs and an invertebrate where sexual reproduction followed by asexual reproduction is found. (Fig. 250.)

The liver fluke, *Fasciola hepatica*, another member of the flatworm phylum (Platyhelminthes) to which the tapeworms belong, is an important parasite producing a serious infection in sheep. The adult stage of the liver fluke occurs in great numbers in the liver of the infected animals and is seen as a small, flattened, disc-shaped structure without noticeable external organs. The adults are hermaphroditic and produce gametes in great numbers. The fertilized eggs pass down the bile duct, into the alimentary canal, and the partially developed embryos are egested with the feces. They cannot survive more than a few hours unless they find their way into water. If their quest is successful, they quickly develop into tiny, ciliated bodies, the *miracidia*, whose survival is dependent upon finding their next host, which is a particular species of fresh-water snail. If the snail is found, the miracidia bore their way into the soft tissues and then by utilizing nutritive materials from the host begin to grow rapidly. Parthenogenetic reproduction occurs repeatedly with the formation of several types. Finally, great numbers of parasites, all asexually produced from the miracidia, leave the snail as active *cercariae* and endeavor to attach themselves to stalks of grass. Here they encyst and await introduction into the sheep when the infected grass is eaten. (Fig. 251.)

Finally, it should be recognized that parasites are, in turn, parasitized themselves, and so they serve as the host for other species of parasites. This condition, known as *hyperparasitism*, is possibly most clearly in evidence among the insects, where it is often used to advantage by the entomologist of today in the endeavor to control insect pests that parasitize important plants. The introduction of another organism that will parasitize the injurious insect may serve to control the spread of the latter. An example of hyperparasitism, the tussock moth, may be cited. In the larval, or caterpillar, stage this insect feeds upon the leaves of trees and causes great destruction. The entomologists know of more than 20 insect species that are adapted for securing their nutrition by parasitizing the tussock moth. These are known as *primary parasites*, and some of them have been found of value in controlling the destructive activities of the tussock moth, when introduced under proper conditions. But the primary parasites have secondary parasites and so on ad infinitum, as the old rhyme goes. For the smallest insect species are often parasitized by unicellular protozoa and bacteria, parasite on parasite forming one of the innumerable food chains in nature, all based ultimately on the utiliza-

tion of the green plant tissues. It might be thought that the chain of parasitism ends with the extremely minute bacterial cells, but, in late years, it has been shown that the bacteria are attacked by the

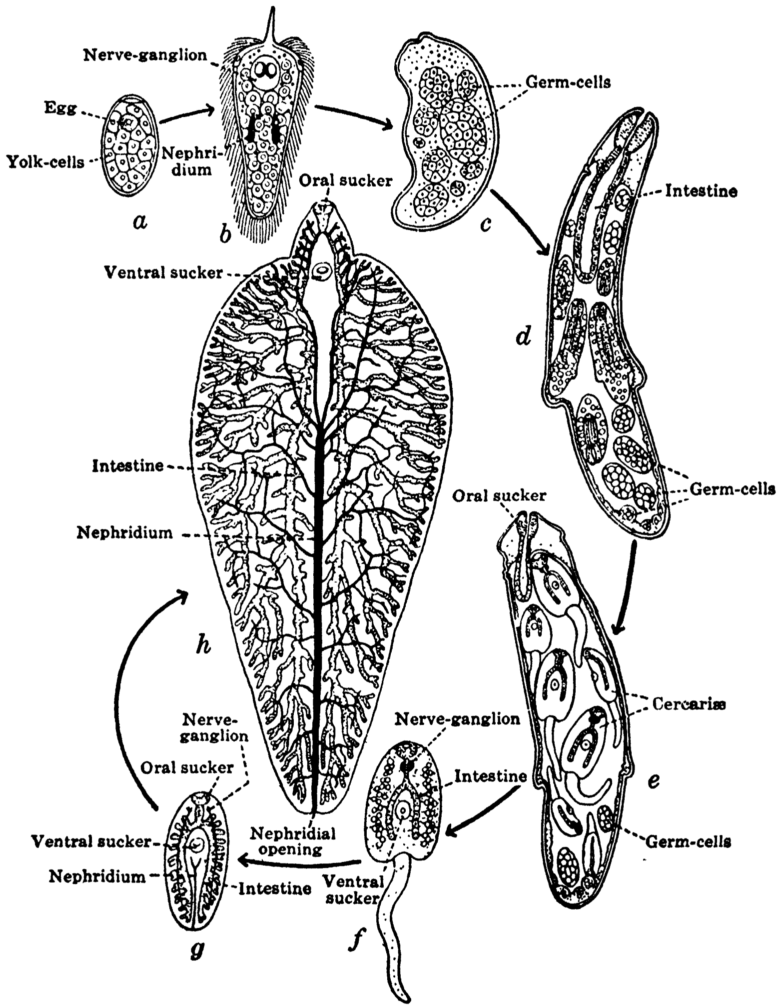


FIG. 251.—Diagrams illustrating the life cycle of the liver fluke (*Fasciola hepatica*) parasitic in the sheep, as described on page 465. *a*, egg; *b*, miracidium which enters snail and produces stages *c-f* asexually; *c*, sporocyst; *d* and *e*, rediae; *f*, cercaria developed in rediae; *g*, inactive stage encysted on grass; *h*, adult stage in sheep's liver. (*Hegner, after Kerr.*)

very much smaller ultramicroscopic units of the bacteriophage which, like the viruses, are below the cellular level in organization and apparently at the vague border line between living and nonliving.

CHAPTER XVII

BIOLOGY OF DISEASE

The consideration of parasitism in the previous chapter leads naturally to the problems associated with disease, for an infectious disease is always the result of an invasion by some parasite. Only in comparatively recent times has this condition been fully recognized even by the scientist; as a matter of fact, it is still unrecognized by the great majority of people living outside the sphere of scientific knowledge. Among the latter, the age-old demonic theory of disease still holds sway. This theory is based on the belief that disease is due to the indwelling of sundry evil spirits and that recovery is, therefore, to be expected when the demons are forced to leave the body of the unfortunate victim. The recent hex trials in a neighboring state emphasize the fact that there is no necessity for looking to some remote, uncivilized region in order to find adherents to this ancient belief of the origins of disease.

Numerous other theories of disease have been proposed during the ages that have passed since attention first began to be focused on this problem. In the present discussion, it will be possible to mention only two or three of these. Thus there is the theory of the humors taught by that illustrious father of medicine, Hippocrates.[1] He reached the conclusion that disease was due to an improper mixture of the four hypothetical body fluids, or humors, namely, blood, phlegm, yellow bile, black bile. Another theory of disease which was widely held for a time, and possibly still has its adherents, is the terrestrial disturbance theory which was notably espoused in this country by that illustrious student of the English language Noah Webster. This theory held that disease was the result of violent terrestrial disturbances, ranging from windstorms to earthquakes. As a matter of fact, it is entirely evident that epidemics of disease do tend to follow disturbances of one kind or another, but it is also clear that the epidemics which appear under these conditions are the indirect and not the direct result of the preceding disturbances. For these catastrophes make possible the wide distribution of parasitic disease-producing organisms, and the latter, under the disturbed conditions temporarily present, find it possible to incite widespread epidemics.

[1] Consult Appendix: Biology and Medicine; Hippocrates.

Then there was the famous Hahnemann theory of disease which taught that disease results from the "derangement of a spiritual vital principle," whatever that phrase may mean. Hahnemann used as treatment for diseases a great many natural substances, highly unusual and obscure in nature, which were prepared for use by repeated dilution and shaking. As a matter of fact, the methods of Hahnemann undoubtedly represented a great advance over the treatments for disease prevailing at that time, for many of the prescriptions in general use by the physicians were virulent concoctions essentially dangerous, which had been handed down over long periods of time. Apparently each succeeding generation of physicians had felt free to add other doubtful ingredients to the prescriptions until it almost became a fact, as stated by Oliver Wendell Holmes, that "if all the drugs that had ever been used for the cure of human ills, were gathered together and thrown into the sea, it would be ever so much better for humanity and ever so much worse for the fishes."

It was not until after the middle of the last century that the many and highly varied theories of disease were finally directed into a definite channel. This was primarily due to the work of Louis Pasteur, who, to quote a recent author[1]:

> . . . by the brilliance of his genius, by the clearness and breadth of his vision . . . formulated the bacterial or germ theory of infectious diseases which must forever dominate medicine. No longer could evil spirits be held responsible for disease nor could an improper mixture of the four humors be regarded as the cause of ill health. Disease was but another example of the struggle for existence; it was life preying on life; the invasion of the macroörganism by the microörganism. The cause of typhoid, cholera, diphtheria, tuberculosis, meningitis, and many other diseases have today passed from the realm of theory into the field of established fact, and each year finds the list of vague indefinite diseases growing shorter and the list of germ diseases longer.

NONINFECTIOUS DISEASES

Thus far, our discussion has been concerned with infectious diseases which result from the invasion of a living parasite. It must be recognized, however, that many important diseases are not communicable—that a disease may be produced in the body by various factors that do not involve attacks by living agents. But the diseases so produced are necessarily localized in one individual only; there is no possibility of direct transfer of an infective agent to another individual. It will

[1] Quoted by Greaves, "Elementary Bacteriology," p. 349, W. B. Saunders Company, Philadelphia, 1928.

be helpful to indicate the nature of a very few noncommunicable diseases at the present time. Outstanding examples may be noted in the various dietary deficiency diseases which, as we know, have their origin in diets that do not contain all the essential nutritive materials. In particular, in the last few years, a great deal of attention has been given to securing diets adequately balanced with respect to the vitamins (page 57). The establishment of the direct relationship between vitamin deficiency and serious pathological conditions has worked a revolution in dietary questions the world over.

But it is also very apparent that vitamins are not the only materials that may be lacking from an apparently adequate diet. For example, it was noted in the earlier chapter on Secretion that lack of iodine in the diet restricts the thyroid gland in its production of the thyroid hormone thyroxine; and this, in turn, is responsible for the cretinous condition (page 106). Numerous other noninfectious diseases may originate through functional abnormalities, such, for example, as athlete's heart or kidney failure. And there is a whole host of physical and chemical agents in the environment which injure the cells in various ways and thus induce disease. Further consideration would take us too far afield, but it should be clearly recognized that whether a disease is parasitic in nature or is produced by some other abnormal condition as just noted, it is always definitely associated with and localized in some group or groups of cells. All the functions of the body, whether in health or in disease, are the result of cellular action; and if these cellular activities are abnormal, then we have disease. Thus it is evident from the biological standpoint that the picture presented by any disease results from the adaptation of the affected cells to the pathological conditions and their attempts to repair the damage and to regenerate new tissues in the injured areas so that normal activities may be resumed.

IMMUNITY

The host is not defenseless in the warfare inaugurated when parasitic organisms attempt to invade the tissues of the body. The foundation of the host defense is believed to center around the presence of specific chemical substances, the antibodies, some of which appear to be always available, whereas others are not formed until the invader actually enters the host tissues. An antibody wages chemical warfare on the parasite, and accordingly the invader may be limited in its activities or entirely destroyed. It has long been recognized that immunity to a particular disease-producing parasite may be inherent or, in other words, a species characteristic (natural immun-

ity) or it may be acquired by experiencing the disease (acquired immunity). Presumably the most important factor in either natural or acquired immunity is an antibody reaction. On this basis, natural immunity is present when an organism inherently possesses an antibody against the disease in question; acquired immunity, when the organism is forced to synthesize a specific antibody, following the attack of the parasite, in order to survive. The antibody once formed in the host may remain and thus render the environment permanently unsuitable for the activities of that particular parasite. In other words, the individual possesses an acquired immunity.

Perhaps the situation may be clarified by one or two specific examples. Thus, typhoid fever is a dangerous disease to which the human species is very susceptible, but the domesticated animals, with which man is closely associated, have a natural immunity. Typhoid is due to a bacterial invasion which centers primarily in the mucosa lining the alimentary tract. The typhoid bacteria gain entrance by the ingestion of infected foods. In the alimentary canal of the dog, however, there is a natural immunity and the typhoid organism is unable to secure a foothold; the ingestion of food materials bearing the typhoid bacteria has no ill effects. But the reverse is true for distemper, a virulent disease in dogs which invades the body tissues by way of the respiratory tract. Man, fortunately, has a species, or natural, immunity to this disease.

Even though a species may be susceptible to the attacks of a disease-producing organism, some groups or races included within the species may have a natural immunity. Even individuals within these subdivisions show marked variation in either direction; that is, they may be more resistant or less resistant than other individuals in the group. Thus none of the disease epidemics so far encountered by the human species has been able to infect every individual. If it had been otherwise, man would long since have been swept from the earth as a result of epidemics that have appeared in past times. The Negro race is much more resistant to yellow fever than are members of the White race. Eskimos as a group are particularly susceptible to tuberculosis, and the same condition obtains with reference to influenza and certain other diseases, such as measles, among the South Sea Islanders.

As is well known, susceptible individuals commonly acquire an immunity against further attacks by experiencing the disease. This naturally acquired immunity is frequently of a permanent nature. Unfortunately, however, a number of infective diseases do not give the victim a permanent immunity. Such is the situation following

attacks of the common respiratory diseases, including various types of colds and influenza that afflict the human organism. Even the much more serious invasion of virulent pneumonia parasites does not grant immunity against later infections to those who were fortunate enough to survive the first attack. For the great majority of diseases, however, the survivor unquestionably does acquire immunity, be it temporary or permanent. The underlying basis for immunity acquired by the individual is believed to center in the antibodies developed in the host as a result of the parasitic invasion and which remain temporarily or permanently to ward off later attacks.

But the fact to be emphasized in our present consideration is that laboratory methods have been developed by the researches of specialists in this field, the immunologists, that can be used to confer an artificial acquired immunity without experiencing the disease. These immunological methods are of such fundamental importance for the control of infectious disease that it will be worth while to give them full consideration. In the first place, it should be emphasized that whether immunity against a particular parasite is naturally acquired by having the disease or by treatment with established artificial methods, it is the presence of a specific antibody that is the basis of the immunity. The production of an antibody may be incited either in the tissues of the individual desiring immunity (active immunity) or in the tissues of certain other animals that have been found suitable, such as the horse or goat, and then transferred to the human organism for conferring immunity (passive immunity).

Considering, first, the active type of artificial acquired immunity, which, as just noted, involves the formation of antibodies in the body tissues just as when a particular disease is experienced, it is found that the antibody response is invoked by inoculation or vaccination with the actual living parasitic organisms. However, the virulence of the latter has been reduced by special methods so that the individuals vaccinated do not experience so severe a case of the disease as would occur if they were inoculated with fully active organisms. The reaction of the body tissues to the attentuated organisms is, however, sufficient to confer active immunity through antibody formation. The best known example of an acquired active immunity is that conferred by vaccination against smallpox, which will be considered later.

An acquired passive immunity is the result of a treatment in which the antibody against a particular disease has been developed in some suitable experimental animal and then transferred to the human organism by way of the blood serum. This is particularly well shown in the antibody used in the fight against diphtheria. Diphtheria anti-

toxin is synthesized in the horse and then transferred to the human organism for use in developing immunity in children or even for the treatment of diphtheria if it has unfortunately been contracted. Passive immunity of this type is typically less permanent than is active immunity.

ANTIBODIES

Frequent mention has been made in the paragraphs above of the ability of antibodies to combat invading parasites and also to confer active or passive immunity. Thus the valuable functions of the antibodies are recognized even though very little is actually known as to their chemical nature or as to how and where they are synthesized in the animal tissues. It is generally recognized that there are four main types of antibody reactions, any one of which may be called forth following the entrance of parasites or other foreign substances into the host tissues. Presumably, there are four types of antibodies corresponding to the different types of reaction. These are designated as the *antitoxins*, the *opsonins*, the *agglutinins* or *precipitins*, and the *lysins*, and may be considered in the order named.

Antitoxins.—The term *antitoxin* given to this group of antibodies indicates that they react against and thus neutralize the poisonous substances (toxins) formed by a parasitic organism in the tissues of the host. The damage wrought in certain diseases, notably diphtheria and tetanus, is due to the action of a toxin given off by the parasitic agent. It is also a function of the antitoxins to neutralize injurious foreign proteins which gain entrance to the body tissues in various ways, as happens for example, when venom is injected by the snake bite.

Opsonins.—The term given to this type of antibody is derived from a Greek verb meaning "to prepare food." The term refers to the action of the opsonins in modifying the invading bacterial cells so that they become "palatable" to the phagocytic leucocytes of the blood. The latter readily ingest and destroy bacterial cells following their contact with an opsonin. The phagocytic reaction may be observed under a microscope, as described later.

Agglutinins.—The name refers to the ability possessed by this group of antibodies to cause the permanent clumping together, or agglutination, of bacterial cells and thus to bring about their destruction. Presumably the agglutinin reactions cause chemical changes at the surfaces of bacterial cells. As a result, the cells stick together when they come into contact, and so great numbers become inseparably associated, forming large irregular masses. Closely related to

the agglutinating reaction of living cells is the important precipitin reaction, presumably incited by the same type of antibody, which is visibly indicated by the formation of an insoluble precipitate when a specific protein in solution is encountered by the antibody. A precipitate is built up by the adherence of ultramicroscopic protein molecules to form visible particles.

Lysins (Cytolysins).—This group of antibodies is responsible for the most powerful and complex reactions of all. The lytic reaction causes the destruction of an invading cell through an actual disruption of the cell wall which results, in turn, in the dispersal of the protoplasmic content. Commonly, lysins act as destroyers of bacterial cells and are known, therefore, as the *bacteriolysins*, but of great importance in diagnosis are the hemolysins which cause the destruction (hemolysis) of red blood cells. The hemolysins are the basis of the so-called complement-fixation tests which are of primary importance in the Wassermann test, as indicated below. Lysins are characterized by the fact that they have two combining affinities: first, with the invading type of foreign cell and, second, with an obscure substance, the complement, normally present in the blood plasma. The combination of lysin, foreign cell (antigen), and complement results in lysis, that is, the destruction of the antigen.

Though it has generally been held by most authorities that four different types of antibody are active in the endeavor to destroy invading cells or foreign substances, as just described, the so-called unitarian viewpoint has been increasingly emphasized in recent years. It holds that only one basic type of antibody is formed in the animal body but that this powerful substance has the possibility of functioning in the four different ways just indicated, that is, as an antitoxin, an agglutinin, an opsonin, or a lysin. For the present discussion, the question is not of primary importance since the results are the same in either case.

IMMUNOLOGY: USES AND TECHNIQUES

The fact, as shown in the earlier discussion, that immunity to various dangerous diseases may be obtained through the use of artificial methods involving antibody formation, so that the individual does not need to experience the disease, has led to a very rapid development of a new science, Immunology. It is also increasingly evident that the methods employed in this field have important applications outside the medical field. The present situation may be briefly summarized as follows:

1. It is possible to determine by immunological methods whether or not a person possesses a natural immunity to certain diseases. This

is best exemplified by the well-known Schick test for diphtheria, described below.

2. It is possible, by the use of various immunological methods, to acquire immunity to some of the worst diseases known to man. Thus, if the Schick test shows that a child is susceptible to diphtheria, artificial acquired immunity may be obtained through the proper treatments.

3. To a limited extent, it is possible to cure diseases through immunological methods. The outstanding example again is diphtheria, but progress has been made with pneumonia, scarlet fever, dog distemper, and other diseases.

4. Immunological methods are increasingly important in the medicolegal field, for they are able to solve problems dealing with the identification of various proteins. This is particularly important in the identification of blood stains.

5. Diagnosis of disease has been greatly advanced by the use of the proper immunological methods. This field has become of particular importance in the diagnosis of veneral disease, and the result is shown by the laws passed in an increasing number of states requiring that freedom from such disease be established by these diagnostic tests previous to the granting of a marriage license. For example, the present law in Connecticut is as follows:

> No application shall be accepted by the registrar until he has in his possession a statement or statements signed by a licensed physician that each applicant has submitted to a Wassermann or Kahn or other similar standard laboratory blood test and that, in the opinion of the physician, the person is not infected with syphilis or in a stage of that disease that may become communicable and such statements shall be accompanied by a record of the standard laboratory blood tests made, which record shall contain the exact name of the applicant.

The immunological methods are dependent upon reactions that occur in the liquid blood serum. It will be remembered from the discussion in an earlier chapter (Chap. VII) that blood consists of various types of blood cells and a liquid plasma in which the cells "live and move and have their being." It was also shown that the phenomenon of clotting is a function of the plasma. Following clotting, a non-coaguable liquid, the blood serum, is squeezed out of the clot by the gradual contraction of the fibrin elements. Blood serum is of primary importance in immunology, for it contains the antibodies that may have been developed in an individual as the result of parasitic infec-

tions or in response to foreign substances that have gained entrance into the tissues. How and where antibodies are formed in an organism is not known, but it is evident that they are finally present in the blood serum.

Securing blood serum from experimental animals involves opening a suitable blood vessel and the insertion of a small glass cannula through which blood will flow into a container. It is necessary to use a technique that will prevent clotting until the blood cells have been removed by centrifuging (page 163). This involves placing the blood in a centrifuge where it is revolved at high speed for a few minutes. The centrifugal force thus developed will throw the blood cells to the bottom of the centrifuge tubes. The cell-free plasma, a straw-colored liquid, is now withdrawn and allowed to clot. The fibrin elements in the clot gradually contract to form a firm, jelly-like mass, from which the permanently liquid blood serum gradually separates. (Fig. 252.)

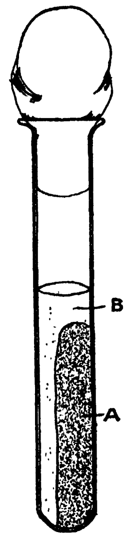


FIG. 252.—Diagram showing test tube with clotted blood. The fibrin (*A*) has shrunken, leaving clear serum (*B*). (*Frobisher, "Bacteriology," W. B. Saunders Company.*)

Now the important thing from the standpoint of immunology is that the antibodies, formed in the organism from which the blood was obtained, are in the blood serum rather than in the cells or fibrin and may therefore be transferred when the serum is injected into another organism. To refer once more to the technique developed for the control of diphtheria: The specific antibody against diphtheria is developed in the horse and then transferred by means of the horse serum to the human blood stream where the antitoxin will be effective against the disease. Essentially this same technique is used in various other immunological activities.

Another example of the serum-antibody relationship is seen in the use of convalescent serum, which is the blood serum obtained from an individual that has had a particular infectious disease and recovered from it. The antibody responsible for the control of the disease remains in the blood serum. Accordingly, the convalescent serum is of value in treating individuals that have contracted the same disease. Possibly the most extensive use of convalescent serum is in connection with infantile paralysis, or poliomyelitis, in which serum obtained from a child who has recovered from the disease is supplied to the one who is ill. The antibody against the infantile paralysis parasite thus fights against the disease when transferred to another individual.

At this point, it will be well to emphasize certain facts relative to the operation of the immunological techniques as a basis for the description of a few representative examples of their use in the control of human disease. In the first place, as emphasized in the preceding paragraphs, an antibody developed in an organism is present in the blood serum and is effective when transferred to another individual. Again, antibody formation occurs in response to the invasion of a particular organism or foreign substance and is a specific reaction to each invader. Finally, it follows from the statement just made that the tissues of an organism must be able to detect an invasion and to react in a specific way to each invader. It is, in essence, the ability to detect a particular protein out of all the possible proteins, almost infinite in number (page 70). This ability of living organisms to detect and react to a foreign substance is almost unbelievable in its specificity.

Hypersensitivity.—Furthermore, a hypersensitivity develops under certain conditions that greatly exceeds the normal immunological reactions in its delicacy of response. This condition of hypersensitivity is technically known as *allergy* (anaphylaxis). An individual may be naturally allergic toward certain foods such as strawberries, clams, eggs, cereals, and even fatty substances. These individual nutritive idiosyncracies, when present, greatly complicate the feeding of children because the ingestion of minute amounts of foods to which they are allergic will cause a violent reaction. Again, individuals may be normal in their nutrition but be highly allergic to certain wind-blown protein particles, such as the pollen from plants or dust of various kinds, particularly from animal hair. This respiratory hypersensitivity is responsible for hay fever and certain types of asthma.

Also, hypersensitivity may be developed in any individual by sensitization to a foreign protein through injection. Thus, as Wells says,

> If the foreign protein is injected into the body of an animal which has been sensitized by previous injection of a minute amount of the same protein, the animal may exhibit a profound reaction, often fatal. Unbelievably small amounts of protein may accomplish this sensitization . . . and hence it serves as a remarkably delicate test for the presence or character of proteins in a solution.

This artificial hypersensitivity developed by sensitization through previous injection of a particular protein is particularly important in immunology.

To take a specific example of this acquired hypersensitivity, reference may be made to serum sickness which results from a previous sensitization to a particular serum, such as horse serum. The horse has been found to be a particularly favorable animal for the development of various antibodies used in the treatment of human disease, in particular, the treatment of diphtheria and tetanus, and is widely used. Accordingly, if a child is given diphtheria antitoxin in horse serum, it may become sensitized to horse serum. At a later time, the child may be so seriously injured that antitoxin protection against the tetanus organism, which produces lockjaw, is deemed advisable. Tetanus antitoxin is also developed in horse serum. Accordingly, if the child has become sensitized, or allergic, to horse serum by the previous diphtheria antitoxin treatment, injection of horse serum with the tetanus antitoxin will cause a violent reaction, serum sickness, which may have serious results.

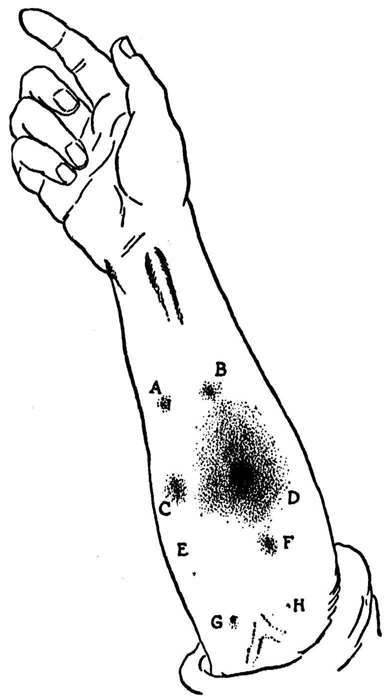


FIG. 253.—Illustrating the reactions in the skin of the forearm after injection of various proteins in a test for allergic substances. The letters indicate the injection of solutions of the following substances: *A*, milk; *B*, protein of pork; *C*, protein of strawberries; *D*, hen's egg; *E*, codfish; *F*, pollen of the rose; *G*, cat dandruff; *H*, pollen of the goldenrod. The test shows that the patient is hypersensitive, or allergic, to the egg protein. The other reactions are not regarded as significant. (*Frobisher, "Bacteriology," W. B. Saunders Company. Redrawn by L. Krause, modified.*)

It is thus apparent that the tissues detect and react almost immediately to a foreign substance to which they are sensitized. Fortunately, a simple test will tell whether or not the individual is allergic to a serum or other substance. This is done by injecting a slight amount in solution under the skin of the forearm. The resulting reaction as indicated by the extent of inflammatory area that develops gives the answer. It is sometimes found necessary to test a great many substances in this way in order to determine those responsible for asthmatic conditions. The phenomena involved in hypersensitivity are by no means entirely clear, but primarily they center around the need of an organism for protection from foreign substances,

particularly if the latter are placed directly into the tissues without having been altered through enzyme action in the alimentary canal. Proteins, in particular, are generally not welcome unless they have entered by way of the alimentary canal and there broken down into their constituent amino acids by the digestive enzymes. In individuals with marked nutritive idiosyncracies, the allergic antipathy is so marked that even entrance into the alimentary canal is sufficient to incite the allergic reactions. (Fig. 253.)

With the general conditions governing immunological reactions in mind, it is next in order to describe a few of the important materials and methods that have been found of value in this field and commonly used by the immunologists in their attempts to eradicate germ diseases.

Killed Cultures of Bacteria.—Since, as stated above, the tissues detect and react to foreign substances, the possibility was early recognized that the injection of the killed cells of a certain disease-producing organism might incite an antibody formation that would give an immunity against living cells of the species injected. An outstanding example of this is found in the development of typhoid vaccine which gives a temporary immunity against this dangerous disease. The striking results that have been achieved are best told by comparing the number of deaths from typhoid in the Spanish-American with those in the World War. In the former, with no typhoid vaccination, there was one death from typhoid for every 71 men, while in the World War, with the soldiers vaccinated against typhoid, there was only one death for every 25,641 soldiers.

Typhoid fever is produced by certain bacterial organisms which cause the formation of ulcers in the lining of the alimentary tract. From these localized regions of infection, the bacteria find their way into the blood stream and thus are widely distributed through the body. In the preparation of typhoid vaccine, the typhoid organisms are grown in pure laboratory cultures by standardized techniques and killed at the proper time by heating. Sterile salt solution is added to make a suspension of the bacterial cells. The number of organisms per unit volume of the suspension is determined so that the correct amount may be sealed in vials for individual dosage. To secure the optimum immunization, three injections of the typhoid vaccine are given; the first dose contains approximately one-half billion bacteria, and the other two, given at later periods, a billion each.

A number of other vaccines prepared in essentially the same manner are in rather common use, particularly for protection against colds and influenza, but the results so far obtained do not give conclusive evidence of their value as does the typhoid vaccine. Possibly this is

to be expected, inasmuch as even severe attacks of such diseases as colds, influenza, and pneumonia do not confer immunity upon the individual. Under such circumstances, it is evident that the use of vaccines to acquire immunity is bound to be of doubtful value.

Living Organisms with Reduced Virulence.—It has long been known that immunity to smallpox may be acquired by vaccination with material containing living organisms having reduced virulence. In 1796, Edward Jenner, an English physician, vaccinated James Phipps, an eight-year-old child, against smallpox by rubbing into a scratch on his arm a tiny bit of infective material from a patient having cowpox. The boy developed cowpox, a disease closely related to smallpox but far less virulent. It was later shown that he had acquired immunity to smallpox by having had cowpox.

This was the start of modern vaccination against smallpox which has proved to be so successful that, in a comparatively short time, it has practically eliminated one of the most dangerous diseases ever known and one that, for untold centuries, took an annual toll of millions of lives. The preparation of smallpox vaccine[1] today is far different, in the rigid controls, from those inaugurated following Jenner's results at the close of the eighteenth century, but the basic principle underlying the treatment remains the same, namely, subjecting the individuals to infection with relatively harmless organisms, thereby inciting antibody formation which will protect against an invasion of highly virulent organisms. The immunity is usually not permanent, and, accordingly, it is necessary to revaccinate every few years to see if the immunity persists. This will be shown by whether or not a later vaccination "takes." Vaccination every 5 to 10 years is essential to insure immunity.

Another example of the use of living cultures of a disease-producing organism is found in the treatment used to prevent hydrophobia following the bite of a rabid dog. This very dangerous disease is produced by a virus that develops slowly in man. Consequently, there is time for the treatment, designed to incite antibody formation, before the rabies organism invades the central nervous system where it produces its deadly effect. The mortality from rabies is stated to be almost 100 per cent when the disease is allowed to run its course, but cure is almost certain when treatment is begun in time. The present treatment is essentially the same as devised by the great Pasteur near the middle of the last century. The modern immunologist knows a great deal more than Pasteur about the principles underlying the immunological reactions, but nevertheless Pasteur was sufficiently well

[1] Consult Appendix: Smallpox Vaccine.

informed to devise a treatment that prevents the onset of rabies. The Pasteur treatment makes use of a vaccine containing the living virus of hydrophia in which the virulence of the virus organism has been greatly reduced by drying.[1]

Antibodies

In the preceding paragraphs, it has been shown how the causative organisms of dangerous diseases, either killed or alive (but greatly reduced in virulence), may be used to incite the formation of a specific antibody in the individual and thus render the environment unsuitable for the development of the organism in question. But in the treatment of certain diseases and also for diagnostic tests, the immunologist has found that it is necessary to have the antibodies formed in experimental animals and then transferred to the human body. This field of immunology, unlike those established by Jenner and Pasteur, has been of comparatively recent development and represents the culmination of immunological research with contributions from scientists in many fields.

Antitoxins.—This group of antibodies, as stated previously, functions in the neutralization of the toxins produced by an invading organism. In certain diseases, notably diphtheria and tetanus, the deadly effects are due primarily to the toxins released in the host by the parasite, rather than to an actual invasion and destruction of a particular tissue. To aid the patient in overcoming certain toxins, it is possible to produce the specific antitoxin needed in the serum of some suitable experimental animal and then transfer it to the human blood stream. The best example of this is found in the development of antitoxin for diphtheria.[2] A child may be seriously ill with this disease and quickly brought back to normal by the proper treatment with a serum containing the antitoxin against the diphtheria toxin. Unfortunately, few diseases can be cured by this method because the foreign antitoxin is ineffective.

Diphtheria antitoxin thus produced in the horse has changed diphtheria from one of the world's worst diseases to its present condition which is indicated by the statement that "no child need have diphtheria." This is due to the fact that it is also possible to determine by the combined use of toxin and antitoxin if children are susceptible and, if so, render them immune. Susceptibility to diphtheria is determined by the now well-known Schick test in which a standardized dose of diphtheria toxin in solution is introduced under

[1] Consult Appendix: Rabies Vaccine.
[2] Consult Appendix: Diphtheria Antitoxin.

the skin of the child's forearm. The extent of the resulting reaction, visible to the naked eye as an inflamed area, is observed. If, as is usually the case, the child is thus found to be susceptible, the toxin-antitoxin treatment is given. This will confer an acquired immunity against diphtheria, which may last a lifetime. The basis for the immunity thus conferred is, of course, antibody formation in response to the diphtheria toxin injected, but it is not desirable to inject this powerful toxin into the human tissues without partial neutralization by the antitoxin. It is probable that in the years ahead the use of antitoxin for the control of various other germ diseases will be greatly extended, but it must be admitted that the results so far achieved limit the applications rather closely to two very important diseases, namely, diphtheria and tetanus. Tetanus antitoxin, furthermore, is effective as a preventative but not as a cure for the disease when the latter has become established.

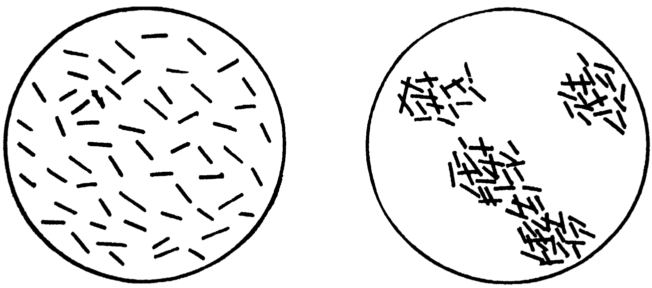
Another increasingly important use of an antitoxin is found in the treatment developed for snake bite. In preparing the antitoxin, the venom is collected from the snakes under laboratory conditions. The venom is then reduced in strength and small amounts are introduced into a suitable animal, such as a goat, which will incite the production of an antitoxin for neutralizing the venom. Goat serum with the antibody is now widely distributed commercially and has proved to be highly efficacious when quickly supplied to the victim of a snake bite. Supplying an adequate amount of the venom antitoxin without delay results in the neutralization of the venom before it has opportunity to destroy the body tissues.

Agglutinins and Precipitins.—In the earlier discussion, it was stated that the agglutinins and precipitins probably constitute a single type of antibody which is characterized by the ability to induce surface changes that cause bacterial cells or protein molecules to adhere and thus build up large clumps or masses. The antibody action is described as agglutination when cells are affected and as precipitation when the phenomenon is associated with molecular changes. Both reactions are of value in various immunological reactions, a few of which will be briefly indicated.

The well-known Widal test for typhoid fever, which is not always easy to diagnose, is based on the action of an agglutinin formed in the tissues of the host following the entrance of the typhoid bacilli. Evidence that the antibody is present may be obtained by noting the reactions between the patient's serum and typhoid bacilli. The serum will contain an agglutinin against typhoid bacilli if the patient is suffering from this disease. Consequently the addition of serum

with the agglutinin to a suspension of typhoid bacilli will give a positive reaction and cause their agglutination, thus forming large clumps of cells. In the absence of the agglutinin antibody, the cells will not adhere. The process can be observed under the microscope when active typhoid bacilli are added to a drop of serum containing the typhoid agglutinin. (Fig. 254.)

Pneumonia is rightly regarded as one of the worst of the infectious diseases. It results from an infection of the lung tissues by various types of pneumococci. Noteworthy progress has been made by the immunologist in its control. In the first place, it has been established that of the four known types of pneumonia, which result from infections by different species of pneumococci, three distinct serological types, known as Types I, II, and III, may be diagnosed by the agglu-



a *b*

FIG. 254.—Illustrating the agglutination reaction with bacteria as in Widal test for typhoid. *a*, normal; *b*, agglutination of the bacterial cells following introduction of the antibody. Highly magnified. (*Greaves, "Bacteriology," W. B. Saunders Company.*)

tination tests. By the use of agglutinins, the immunologist has made noteworthy progress in the control of pneumonia. (Fig. 255.) If the serum reactions show that the patient is infected by pneumococci of either Type I or Type II, beneficial results may be expected from treatment with horse serum containing the corresponding antibody. Serum treatment for pneumonia appears to be of doubtful value when used against Type III infections. It has not been found possible to develop a serum treatment for Type IV. Pneumonia of this type is probably due to a mixed bacterial infection and, fortunately, has a comparatively low mortality rate.

The Agglutinin Tests for Blood Transfusion.—It is often necessary to supply additional blood to a patient who has lost a great deal following some serious accident; or transfusion may be indicated as a result of various diseases, particularly anemia, which is characterized by a marked deficiency of the red cells and, correspondingly, a deficient oxygen supply to the tissues. In the earlier chapter on Human Heredity, it was shown that four types of blood are commonly found

in man and that, in transfusion, the blood supplied to the patient by the donor must be of the proper type (page 409). Otherwise, agglutination of the red cells will occur, and the patient will be injured rather than helped by the transfusion. The clumping of the red corpuscles is due, as pointed out previously, to an antibody reaction. Accordingly it is possible to determine the type of blood present in patient and donor before transfusion. In fact, hospitals find it necessary to have a group of blood donors available, comprising individuals with the various blood types, so that, when a transfusion

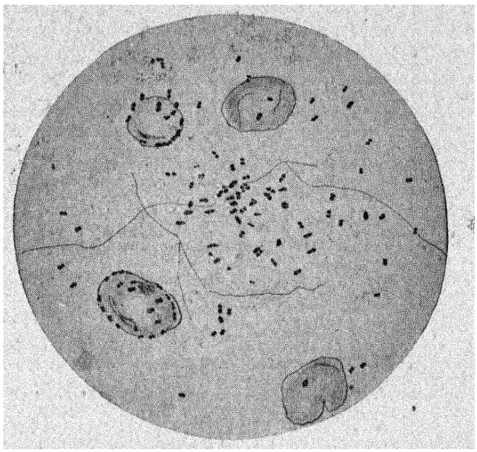


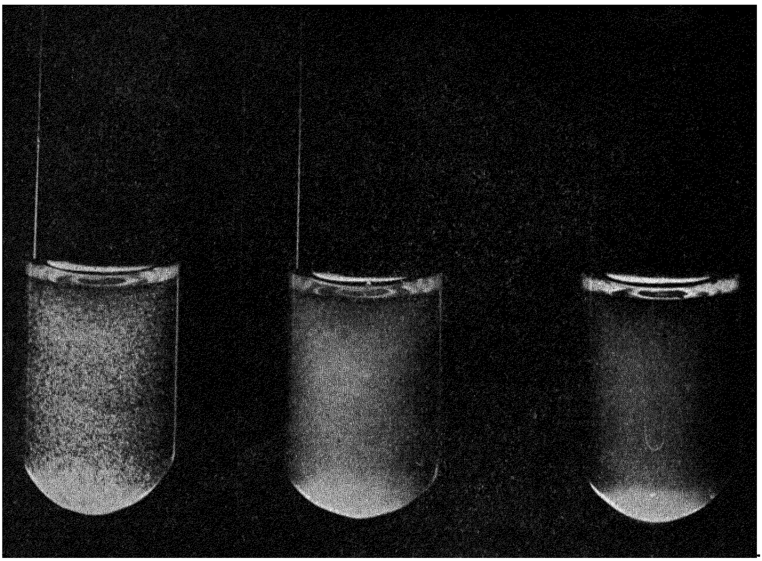
FIG. 255.—Microscopic preparation of peritoneal fluid from a mouse killed by a pneumococcus infection. The numerous pneumococci are seen as black bodies. The large gray bodies are cells. Page 567. × 600. (*Frobisher, "Bacteriology," W B. Saunders Company.*)

is indicated, a donor with the correct blood type can be summoned as soon as the patient's blood has been typed.

Precipitin Reactions.—Increasingly important in various fields of immunology are certain precipitin reactions that, as stated above, result in the formation of a visible precipitate when the test is positive. Such tests are used in medicolegal work when it is necessary to identify certain proteins, blood stains, etc. The test involves the formation in some experimental animal of the specific antibody by repeated injections of the substance that it suspected and the consequent localization of the antibody in the serum. When the latter is matched with a solution of the material to be identified, the formation of a precipitate makes the identification positive.

But the precipitin tests are also of great value for the diagnosis of certain diseases. In particular, the Kahn test for syphilis, which is based on a precipitin reaction, has become increasingly important.

In this test, serum from the patient is tested under the proper conditions with a prepared syphilitic antigen. The presence of the syphilitic antibody in the patient's blood—indicating, of course, that the disease is present—will cause the formation of a visible precipitate when the antigen and serum solutions are mixed. The amount of the precipitate formed is, in general, indicative of the activity of the disease; the absence of a precipitate under the conditions of the test means that no syphilitic antibody in the serum is present, or, in other words, that the patient is free from the disease. (Fig. 256.)



A B C

FIG. 256.—Photograph illustrating the Kahn reaction, a precipitin test. *A*, showing heavy precipitation at bottom of tube which indicates a positive test; *B*, lighter precipitation indicating a positive test, but less virulent; *C*, no precipitation, negative test. (*Kahn, "The Kahn Test," The Williams & Wilkins Company.*)

Lysins.—It is recognized that the lysins are the most powerful group of antibodies and also the most complex in their reactions. It will be remembered that the lytic antibody must combine with two substances before a particular reaction, directed toward the destruction of the invader, will take place. One of these combining substances is a normal constituent of the blood, known as *complement*, or *alexin;* and the other, designated as the *antigen*, may be either invading cells or foreign protein. Lysin is formed only as a result of the invasion by an antigen. The reaction against foreign cells when sufficient lysin has been formed may be indicated as follows:

Complement + antigen + lysin = cytolysis

Cytolysis involves an actual destruction of the invading cells; the cell membranes are ruptured and the enclosed cytoplasm flows out and is destroyed. When bacterial cells are destroyed, the action is known as *bacteriolysis*. One of the most interesting and important of the lytic reactions, because of its use in diagnostic tests, has been developed in the laboratory by the immunologist and is directed towards the destruction of red blood cells (hemolysis). The important thing about this reaction is that, when the walls of the red cells are destroyed, the hemoglobin is released and it colors the liquid in which the reaction occurs, thereby giving visible evidence of hemolysis. The hemolytic reaction is basically the same as bacteriolysis, but it requires the presence of a specific lysin (hemolysin) against red blood cells. The reaction may be indicated as follows:

$$\text{Complement} + \text{antigen} + \text{hemolysin} = \text{hemolysis}$$

Some of the most valuable diagnostic tests at the disposal of the physician are based upon the lytic reactions. These include the Wassermann blood test, which was the first one devised and is still regarded as the standard test for syphilis, though this duty is now shared by the Kahn precipitin test noted above. The lytic tests are generally known as the *complement-fixation*[1] tests because all of them involve the permanent combination or fixation of the complement with lysin and antigen.

EPIDEMIOLOGY

The science of epidemiology is concerned with the nature and the control of infectious or epidemic diseases. The specialist in this field, the epidemiologist, must have broad training in both biology and medicine so as to be able to ascertain the characteristics of the causative organisms and thus be capable of applying the available scientific data for their control. In attacking and striving for the eradication of a parasitic disease, answers must be found to the following problems:

What is the infective organism whose invasion causes the disease? The parasite must be completely identified, its life cycle determined, and the other hosts, if there are any, discovered. The complete morphology and physiology of the parasite during all stages of its life cycle should be ascertained. It is apparent that it would never have been possible to bring about any measure of control of the malaria parasite until it was established that during one stage of the life cycle this organism parasitized a certain species of mosquito, which, in turn, transmitted the disease to man (page 464).

[1] Consult Appendix: Complement Fixation.

What is the portal of entry that the parasite uses in gaining entrance into the human organism? A common entrance to the internal tissues is through the skin by insect bites, as noted with malaria, or through breaks in the skin when wounds occur. In certain instances, but rather rarely, parasites are able to pierce the unbroken skin. This is well illustrated by the hookworm which manages to pierce the soles of the feet. Again, parasites are adapted to gain entrance through the alimentary tract. Amoebic dysentery, typhoid fever, and tuberculosis are notable instances of invasion through this portal. Finally, the respiratory tract is used by a variety of parasitic organisms as a suitable point for beginning their invasion. Colds, influenza, and pneumonia organisms, in particular, make use of this portal.

What are the host-parasite relations? The answer to this question involves a complete study of the nature of the injury to the host tissues; what tissues and organs are affected; how the parasite produces the injury; and how the host reacts to overcome the parasitic invasion.

What methods may be used for determining susceptibility, for conferring immunity; for diagnosis; and, finally, for the treatment of those who have been unfortunate to contract the infection? It is at once apparent that the results obtained by immunologists, as indicated in the preceding paragraphs, are of major importance for the solution of problems in this field. But even so, there are only a very limited number of diseases in which these methods have been found to be completely applicable. In fact at the present time, diphtheria is possibly the only disease in which an answer to all the problems has been obtained by the methods of immunology.

Chemotherapy.—But increasingly important in the treatment of disease are the discovery and use of substances—the field of chemotherapy—that have been found to be specific poisons to a parasitic organisms but, at the same time, essentially harmless to the host. Such substances may be compounds found in nature, or they may be entirely new compounds developed by the biochemist in his laboratory researches. Thus quinine, a natural compound found in the bark of the cinchona tree, is a specific poison to the malaria parasite. On the other hand, the important arsenic compound salvarsan, which is a specific poison for the syphilitic organism, was developed in the chemical laboratory by the extensive researches of the great research scientist Ehrlich. Researches in chemotherapy are constantly yielding results of the highest value for the treatment of disease. One of the latest additions is sulphanilamide and related compounds which

are now widely used in the treatment of various infections because of their lethal action toward the bacterial cells concerned.

As a result of all these advances in immunology and chemotherapy, the great epidemics of infectious diseases, which from the earliest times have swept over the peoples of the world and wrought untold destruction to human life, appear to be past history. The last epidemic of world-wide scope was the influenza epidemic of 1917–1919, and it is still possible that other influenza epidemics may occur, for medical scientists have not yet learned the methods for the control of this infection. But such major plagues of the past as the bubonic plague, yellow fever, diphtheria, smallpox, and malaria appear to be under control except for localized outbreaks. This result has been achieved through the combined researches of scientists in almost every field. Medical science is continually absorbing and putting into practical application the results obtained from research in scientific laboratories all over the world.

TYPES OF CELLULAR RESPONSE

Whatever the type of disease that affects an individual, it appears that relatively few types of cellular reaction are exhibited by the cells and tissues concerned. These standardized reactions are designated by the terms *inflammation, fever, repair, hypertrophy, atrophy.*

Inflammation is the primary and almost universal reaction of the tissue cells to any unfavorable condition. It is essentially a localized response at or near the site of the injury particularly by the elements of the vascular system, so that the region becomes congested with blood fluids and the accompanying cells. An increase takes place in the metabolic activity of the cells; more heat is liberated; and consequently the affected region feels hot or inflamed. In essence, it appears that inflammation is an attempt to localize the disease-producing conditions through the phagocytic action of the leucocytes and by the secretion of specific chemical substances, the antibodies, which are synthesized by the cells concerned. (Fig. 257.)

Fever is a systemic response following a more serious injury to the tissues and one that has not been successfully controlled by the localized inflammatory reactions. In a sense, fever may be regarded as a general inflammation, involving the entire organism and resulting in increased metabolic activity and the consequent elevation of the body temperature, the latter corresponding, in general, with the severity of the infection and resulting injury. High body temperatures are, therefore, regarded with apprehension not because of the fever primarily but because of the underlying condition that they

indicate. Fever involves complicated relations between the vascular and nervous systems, as is clearly indicated by the fact that vigorous exercise results in greatly increased heat production—much more so than does a fever—and yet the body temperature remains normal, for the excess heat generated in the tissues by muscular activity is quickly dissipated at the body surface. The elevation of the body temperature during fever is due to the fact that the comparatively slight amount of excess heat resulting from increased cell metabolism is

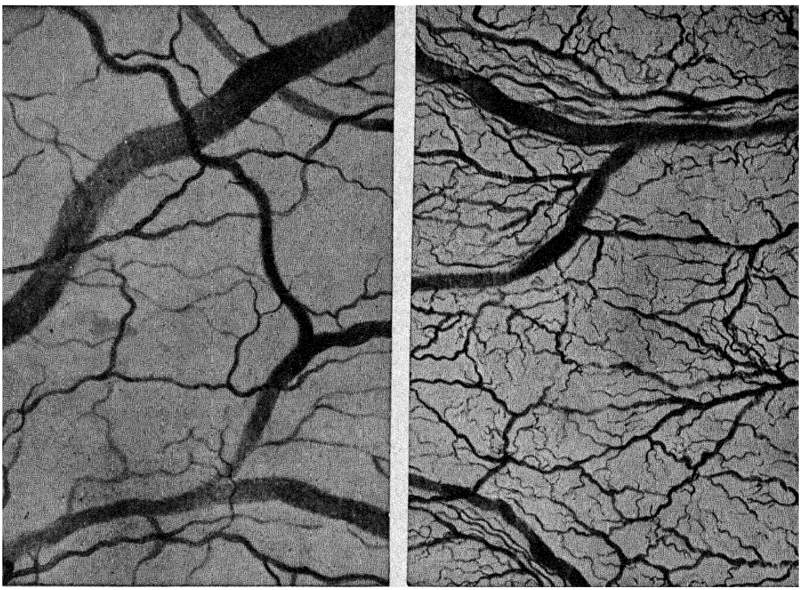


FIG. 257.—Photomicrographs of microscopic preparations of portion of human diaphragm showing contrast in the vascularization in the normal diaphragm (*A*) and in an inflamed diaphragm (*B*). (*MacCallum, "Pathology," W. B. Saunders Company. Slightly modified.*)

largely conserved. The capillaries in the skin are contracted, thereby reducing the flow of blood through them and preventing dissipation of the excess heat at the body surface. This condition is responsible for the common association between chills and fever; the skin feels cold, due to the decreased blood supply, though the body temperature is actually above normal.

Commonly regarded as basically harmful, it has become increasingly evident that, speaking generally, fever is a highly important and beneficial response to an invasion or injury of the body tissues—an attempt to overcome an abnormal condition in the body by destruction of the invader or by the neutralization of poisonous materials through

the production of antibodies. Many of the phenomena associated with the fever reaction remain obscure, but it is evident that they are primarily directed toward the restoration of normal conditions.

Repair is an essential process following the destruction of tissues, whatever be the cause of the injury. Even a slight pinprick, with the resulting local inflammation, is accompanied by a certain amount of tissue injury through cell destruction, so that later when the "fire is under control," the injuries must be repaired and the continuity of the tissues reestablished. Obviously the need for repair is correspondingly greater when more extensive damages are incurred following widespread destruction of body tissues. But repair does not necessarily mean that regeneration of the original type of tissue takes place; the essential thing is that the continuity of tissues be reestablished in the injured area. As a matter of fact, comparatively little regeneration occurs following injury to the highly differentiated human tissues. The loss of lung tissue, kidney tissue, muscle tissue, or even a tooth, to take a few examples, is permanent. The highly differentiated cells are unable to build, to regenerate, additional tissue of the type destroyed. But, if the injured individual survives, the process of repair, by which the continuity of the tissues is again brought about in the affected region, is a necessity. Repair is accomplished through the utilization of the ubiquitous connective tissues, aided, to some extent, at least, by the blood fibrin. The regions of injury are invaded by connective tissue cells which gradually form a wound or scar tissue to serve as a permanent connection between the free surfaces. Thus continuity is established, but the scar tissue cannot supply the functional activities of the original tissue that it replaces.

Usually the cycle involving inflammation, fever, and repair is completed without great delay; but with unfavorable conditions and extensive injury, the restoration of normal activities may be indefinitely delayed. This may result in an overgrowth or hypertrophy of the affected areas, or quite the opposite reaction may occur, in which marked tissue degeneration or atrophy is increasingly evident.

Hypertrophy.—The term *hypertrophy* is used to indicate an overgrowth of tissues to such an extent that a particular region or organ becomes abnormally large. The excess formation of tissue under these conditions is primarily the result of cell growth and consequent mitosis. Certain types of hypertrophy, however, may arise from the accumulation of tissue fluids, as in edema, or from the accumulation of fatty materials stored in the cells of adipose tissue, and in such instances are probably accompanied with little or no actual increase in cell numbers. Hypertrophy is sometimes evident as a very impor-

tant inherent regulatory process by which the organism is able to maintain the normal activities of an essential function, even though an important organ may be missing. Thus, following the surgical removal of a kidney, compensatory regulation is responsible for the hypertrophy of the remaining kidney so that it is able to carry on the excretion of nitrogenous wastes. The same essential process occurs in other organs, as when the loss of one lung results from tuberculosis. Compensatory hypertrophy is particularly evident during embryonic development as can be shown by the experimental embryologist. (Fig. 258.)

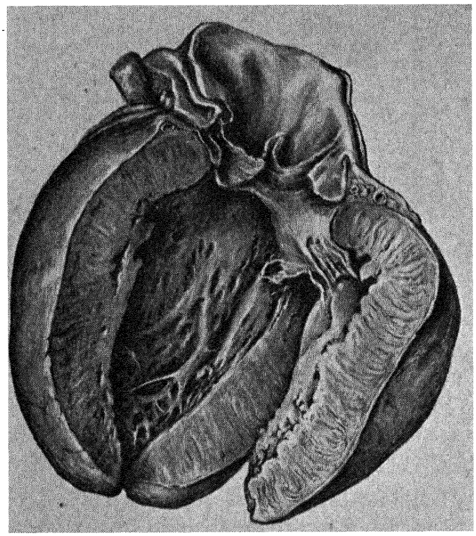


FIG. 258.—Drawing of a human heart showing great hypertrophy of the walls of the left ventricle, which has been laid open. Hypertrophy in this instance was due to increased activity as a result of chronic kidney disease (nephritis). (*MacCallum, Pathology, W. B. Saunders Company. Redrawn by L. Krause.*)

But, specifically, from the standpoint of disease, various instances are found in which hypertrophy is due to widely differing conditions. Thus, hypertrophy may be the direct result of a parasitic invasion. A startling example of this is seen in the widespread tropical disease elephantiasis, which is caused by an invasion of a species of the microscopic roundworm Filaria. The latter, entering the tissues of the legs and feet, gradually accumulate in great numbers in the lymph channels of the legs and thus prevent the normal return of the lymph to the other body regions. The accumulation of the lymph gradually brings about the formation of relatively enormous masses of connective

tissue in the leg and scrotal regions. Again, hypertrophy may have its origin in a nutritive deficiency. Thus, a deficiency in the iodine content is responsible for an abnormal growth of the thyroid. Again, an abnormal functioning of an endocrine gland will result in the hypertrophy of certain tissues, as was previously considered in acromegaly; in this instance a too abundant secretion of the growth hormone from the pituitary gland is the inciting force (page 113). (Fig. 259.)

Atrophy.—This pathological condition is marked by tissue destruction resulting from various causes, to certain of which attention may now be directed. A continued failure to supply the cells of a particular tissue with the proper nutritive materials will necessarily result in degenerative, or atrophic, processes. This nutritive deficiency may

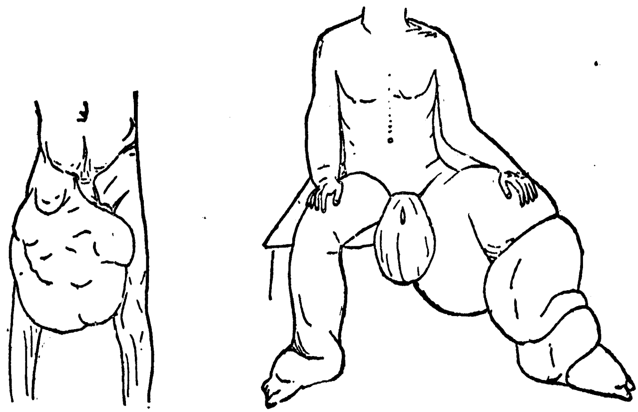


FIG. 259.—Illustrating extreme examples of hypertrophy of the legs and scrotal regions (elephantiasis), the result of filarial infection. (*Chandler, "Animal Parasites and Human Disease," John Wiley & Sons, Inc., after Manson.*)

be caused by a failure to secure the proper foodstuffs or by the inability of the nutritive system to digest them so that assimilation is possible. The same result may occur from a failure of the vascular system to supply a particular area with an adequate flow of blood containing the essential materials; cell destruction must follow. Another striking example of tissue atrophy is found in the degeneration of muscle tissue when the flow of stimuli through the associated nerve fibers is interrupted, owing to section of the nerve or destruction of the neurons. Normal muscle tissue is directly dependent upon its connection with the central nervous system so that muscle tonus may be maintained by the incoming nerve stimuli. An all too common example of muscle atrophy is seen in the degeneration of the leg muscles following severe infantile paralysis that has destroyed the neurons in the central nervous system. Still another source of tissue atrophy is found in the

cumulative action of toxins secreted by parasitic organisms and distributed throughout the body. In addition, there is a great variety of poisonous inorganic and organic substances that may gain entrance to the body and poison the tissues. The concentration may be high enough to produce serious results at once; or with lower concentrations, a chronic toxemia may develop, which results in the gradual atrophy of the affected tissues.

Senescence.—The consideration of atrophy leads naturally to an inquiry as to the real nature of the degenerative changes associated with old age. Is senescence a normal process, or is it essentially a pathological condition? Possibly the gradual wasting away of the body tissues, which is evident in old age, is primarily due to the exhaustion of essential substances or to the accumulation of toxic substances formed in the metabolic processes and not excreted. The biologists have accumulated considerable evidence that such may be the true state of affairs. It has been shown by conclusive experiments with the cultures of paramecium extending over many years, that, given suitable environmental conditions, these cells are able to maintain a continued high rate of growth indefinitely. These results mean that, under the proper conditions, the protoplasm does not become senescent, and the so-called life cycle, which was supposed invariably to end in the death of the organism after a certain number of generations, can be prolonged without limit. (Fig. 260.)

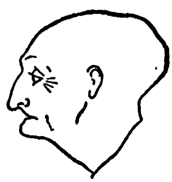


FIG. 260.—Atrophy in old age. "In toothless old age the chin and the nose tend to hob-nob together." (*Walter, after Camper.*)

Of even more interest in this connection is the experimental evidence that senescence can be prevented even in the tissues of highly differentiated, multicellular animals by the use of tissue culture methods. It has been found possible over a period of several years to secure active and continuous growth of connective tissue cells obtained from the heart of a chick embryo. The original fragment of tissue was placed in a culture medium composed of blood plasma and embryonic extract of chick tissues, which proved to be an extremely favorable medium. Now the crucial advantage of this method of cultivating tissues lies in the fact that every few days, or as often as is necessary, some of the actively growing cells from the bit of explanted tissue can be removed from the gradually aging culture, in which the environmental conditions are becoming unsuitable, and transferred to a new culture with fresh culture medium. By this process of subculturing or transplanting from time to time, it is possible continually to subject the cells to a highly favorable environment, and thus,

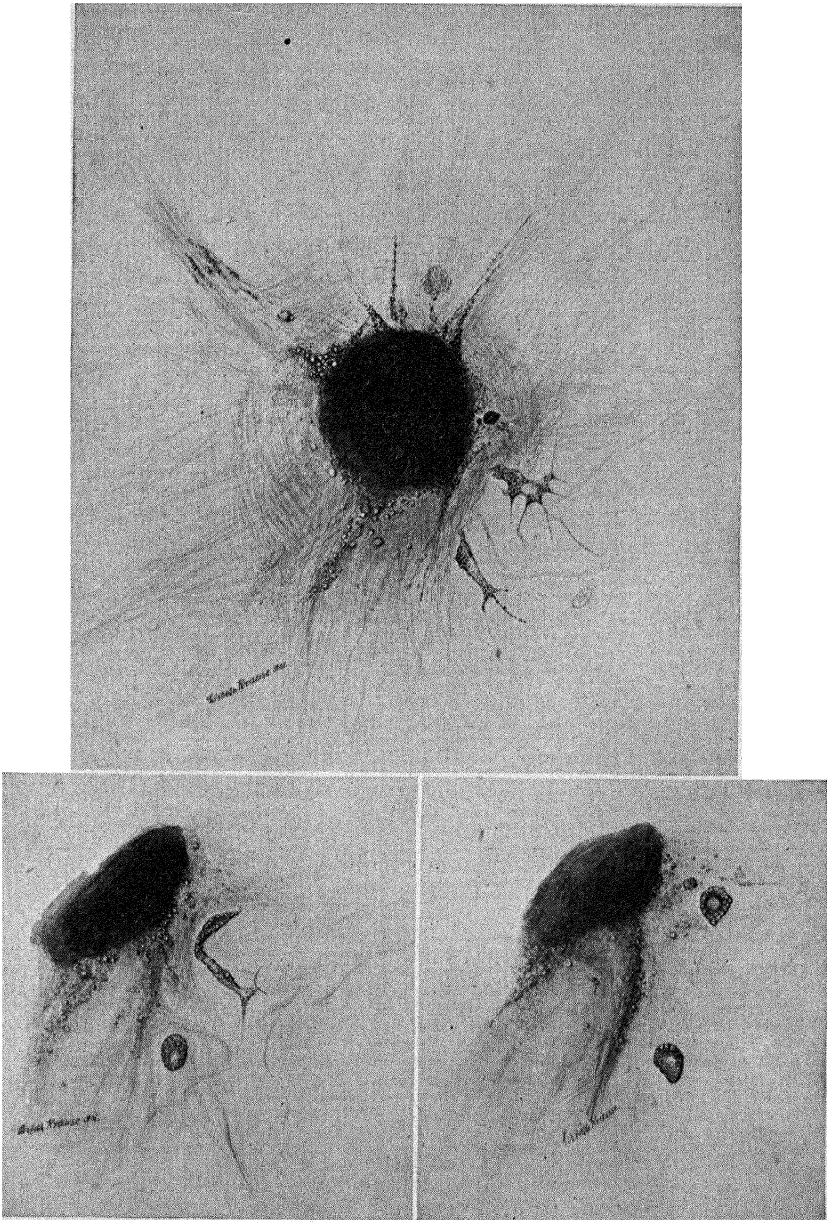


Plate XVIII.—Drawings of a living tissue culture as seen under the microscope. In the upper figure, the dark colored area is a tiny piece of living frog tissue embedded in a drop or so of blood plasma which has clotted. Fibrin filaments are visible. Two large cells (right) are seen which have moved from the tissue into the clot. Later changes in the shapes of these active migrating cells are shown in two lower figures.

apparently, they can be protected from the onset of senescence. (Plate XVIII.)

Attention should also be called to the fact that the germ cells of all organisms possess a method by which they remain young and embryonic in character, although the somatic cells of organisms that produced them gradually become senescent. The complicated processes of germ cell development in the two sexes result in the formation of the highly specialized male and female germ cells. And the extraordinary thing is that by the union of these two cells, a composite cell is produced in which the protoplasm is apparently as young as the first protoplasm on this earth and a cell that has the potentiality of gradually producing a complete new organism through growth and differentiation. Biologists have no experimental data to show how the germ cells are able to carry on in this matter, while, in the same environment that nourished them, a gradual aging and senescence of the somatic cells occurs; and although we are not on proved ground in attempting to explain this inherent ability of the germ cells to bridge the generations, it appears reasonable to suppose that the primary factor lies in being able to break away from the gradually aging body in which they were produced and to secure a new and more favorable environment.

It appears from the foregoing data that the suitability of the environment may be of fundamental importance in determining whether or not senescent changes are to appear in animal cells. On this basis, then, senescence is to be regarded not as an inherent characteristic of protoplasm but essentially as a pathological condition incited by unfavorable environmental conditions. Possibly the unsuitability of the environment in a highly specialized animal is due to some slight, but accumulative, deficiency of substances essential to the cell metabolism. Or, again, the possibility exists that senescence is due to imperfect excretion, thus resulting in a gradual accumulation of the excretory products and a consequent increasing restriction of the normal life processes as the wastes accumulate. At all events, we are not in a position at present to do more than indicate certain possibilities. Death is still certain.

APPENDIX

Abiogenesis. The term used to designate the discarded belief that living matter arises spontaneously from nonliving matter. See Biogenesis. Organic Evolution.

Acetylcholine. "These observations have seemed to us to lead inevitably to the conclusion that, in spite of the considerations which made the idea initially difficult to entertain, the excitatory process is actually transmitted across a synapse in an autonomic ganglion, by the liberation of acetylcholine as the impulse reaches the endings of the preganglionic nerve fibres. With regard to the mechanism by which acetylcholine is thus liberated from the inactivating and protective complex, in which we must suppose it to be held in the neighbourhood of the preganglionic nerve ending, Brown and Feldberg (1936b) have made the very suggestive observation that, if the potassium content of the perfusion fluid is suddenly augmented, acetylcholine promptly appears in the venous effluent from the perfused ganglion, in a manner strongly reminiscent of its appearance when the preganglionic nerve is stimulated. There is evidence connecting the propagated impulse along a nerve fibre with a wave of mobilization of potassium ions; and it is tempting to picture this process arriving at the ending of the preganglionic fibre, there immediately liberating a small charge of acetylcholine, which causes the discharge, from the nerve cell sensitive to its action, of a new propagated impulse, perhaps a new wave of potassium mobilization, passing along the postganglionic fibre."

. . . .

"The case of the voluntary muscle presented additional difficulties. A sympathetic ganglion is a small structure, and the synaptic endings of preganglionic fibres are closely packed in it. If acetylcholine were liberated by the arrival of preganglionic impulses at these endings, we might expect to find it in reasonable concentration, in the fluid slowly percolating through the very small vascular bed of the ganglion; and my colleagues had, in fact, so found it. In the voluntary muscle, on the other hand, the motor nerve endings are thinly scattered, one to each fibre, through a relatively enormous mass, and only a very small part of the perfusion needed to keep the muscle alive makes any contact with them. If acetylcholine were liberated at these endings by the arrival there of motor nerve impulses, we should, accordingly, expect to find it, if at all, only in very low concentration in the fluid flowing rapidly from the vein. The concentration which we found was small, indeed, but not too small to be detected and measured by the delicate physiological tests available. The substance so detected showed the physiological activities of acetylcholine, not only on one test object, but in the characteristic proportions on several, including some reacting to its "nicotine" and others to

its "muscarine" effects. It was rapidly destroyed by cholinesterase or by alkali; there could be no reasonable doubt, indeed, as to its identity. Though the quantity obtained was small, it was of the order to be expected. Calculating, as in the case of the ganglion, the quantity liberated in a muscle by a single, maximal motor volley, and then, from the number of muscle fibres, the quantity liberated by one impulse arriving at a single motor nerve ending, we obtain a number of the same order as that obtained for a single impulse impinging on a single ganglion cell, namely 10^{-15} gramme, or about 3 million molecules." (Quoted from an article by Sir Henry Dale, entitled "Transmission of Nervous Effects by Acetylcholine," which is printed in *The Harvey Lectures*, Series 32, pp. 237–239, Williams & Wilkins Company, Baltimore, 1937.)

Adrenal Glands—Historical. "During the fifteenth century, as one phase of the revival of learning, a novel fashion sprang up in the field of medicine. It became the vogue to consult nature rather than the old Greek authorities. The human body was subjected to a new scrutiny from head to heel. From this scrutiny emerged the recognition of numerous structures, the names of which still serve as monuments to their finders. Among the scholastic radicals, one of the most eminent was Eustachio. His name is perpetuated as the first to describe the passage leading from the throat to the inner ear—the Eustachian tube. It was he who also—in the year 1563—reported the discovery of the adrenal (suprarenal) glands. With the recognition of their existence and such a description as naked eye observation permitted, however, progress ceased. Many a slow step in the development of biologic methodology had to be taken before the first inkling of their functions emerged. The experimental method, to which medicine chiefly owes its modern progress, was introduced by John Hunter only in the late seventeenth century. Prior to that time, clinical experience was seldom productive of anything more substantial than uncritical lore. Physiology mostly consisted, as it had for centuries, of picturesque speculations. Some of these are well illustrated in the story of the adrenal itself.

"In 1716, as Sharpey-Schafer tells the tale, the Academy of Sciences of Bordeaux proposed as a subject for competitive essays: 'What is the Use of the Suprarenal Glands?' The manuscripts were submitted for judgment to the young president of the society, the budding satirist, Montesquieu. In a spirit foreshadowing his future renown, Montesquieu reported 'Some have imagined that these glands are placed in the situation where they occur in order to hold up the stomach which would otherwise press too hard on the veins of the kidneys. Others have imagined them to strengthen and consolidate the venus complex which is in contact with them—conclusions which have appeared to escape the ancients who were content with simply expressing ignorance of the functions of these glands. Bartholin was the first to relieve them of the stigma of performing so menial an office. He is of the opinion that a humour which he terms 'black bile' is preserved within their cavity and believes that there exists a communication between the capsules and the kidneys, this humour serving to dilute the urine.

"'Some anatomists teach that the only use of the glands is to collect the humidities which leak out of the great vessels surrounding them; others have held that a bilious juice is formed within them and being carried to the heart mingles with acidity which is there present and excites fermentation, this being the cause of the heart's movements. Others consider that the humour within the glands is nothing more than a lacteal juice which is distributed by the mesenteric glands.

"'We have one author who affirms the existence of two kinds of bile, one, grosser, secreted by the liver; the other more subtile, secreted by the kidneys with the aid of a ferment. This ferment flows from the glands through ducts, the existence of which is completely unknown to us—and as to which we are threatened with perpetual ignorance,' adds Montesquieu. Finally confiding his opinion that none of the memoirs submitted could be looked upon as satisfying the legitimate curiosity of the Academy, he concludes: 'Perhaps chance may some day effect what all these labors have been unable to perform.' Nearly a century and a half elapsed before that chance was realized." (Hoskins, "The Tides Of Life," pp. 25–27, W. W. Norton & Company, Inc., New York, 1933.)

Aerobes and Anaerobes. "With respect to these sources of oxygen it may be said that there are two main classes of bacteria. First, there are the *aerobic* bacteria which, like most other creatures, utilize the oxygen of the air. Some of these cannot grow at all well unless perfectly free access to air is had at all times. These are called *strict aerobes.* Second, there are the *anaerobic* bacteria which can live and grow in the *absence of free oxygen.* Some species of anaerobes are extremely sensitive to the presence of air and will not multiply at all if the least trace of oxygen be present. Some are so sensitive that a few minutes exposure to the air kills them. These are called strictly *anaerobic* bacteria or *strict anaerobes.* . . .

"Although strictly anaerobic bacteria thrive best only in the absence of free oxygen, it must not be supposed that they differ from other living creatures in not requiring oxygen for growth. It is only that they are sensitive to *free* oxygen. In anaerobic metabolism, whether by strict or facultative anaerobes, oxygen is believed to be obtained through the hydrolysis of carbohydrates, and also of nitrogenous compounds such as proteins. Substances like sodium nitrate are also easily reduced by many species. Such reactions may proceed according to the following equation:

$$NaNO_3 = NaNO_2 + 0.$$

"The oxygen thus obtained may be utilized directly in oxidating some other substance inside the cell. This yields energy. The process of taking oxygen from one molecule requires energy, but more is gained when the oxygen is used to oxidize some other compound. Furthermore, by hydrolyzing carbohydrates and proteins, oxygen may be taken from one readily reduced part of a hydrolyzed molecule and used to oxidize another radical of the same molecule. This results in a liberation of energy to the bacteria through the

formation of a less highly oxidized compound; a molecular rearrangement having occurred to permit this, the bacteria gaining energy thereby." (Frobisher, "Fundamentals of Bacteriology," pp. 47, 48, Courtesy of W. B. Saunders Company, Philadelphia, 1937.)

Alternation of Generations. The alternation of sexual and asexual generations in the life cycle of an organism. In the plant kingdom, the phenomenon is widespread and is exhibited by all the higher plants. Many examples occur also in the animal kingdom, notably among the Coelenterates. The classic example is found in Obelia in which the asexual generation is a sessile, branched, colonial form. Buds are formed asexually which develop into tiny jellyfish (medusae). These are detached from the parent organism when mature and become free-swimming sexual individuals. Sperm and eggs formed by the medusae are released into the water, fertilization occurs, and the zygote develops into the asexual colonial stage. (See Coelenterata.)

Amino Acids. Nitrogenous compounds that are associated to form proteins. They are characterized by the presence of the NH_2 group (amino group). See Proteins.

Amoeba. "There is probably no better introduction to the study of the biology of an animal than that afforded by *Amoeba proteus*, a common organism of ponds, ditches, and decaying vegetable infusions. Amoebae, frequently referred to as the simplest animals, are representatives of the great group of single-celled animals, or Protozoa. Members of this group are found in almost every niche in nature and, like the Protophyta, as the unicellular plants are sometimes called, are important because, although small in size, the number of individuals is inconceivably large. Collectively, they produce profound changes in their environment.

"In order to study an Amoeba it is necessary to magnify it several hundred times. This done, it appears as a more or less irregular mass of granular jelly-like material, rather slowly changing its shape and thereby moving along. As a matter of fact it is essentially a naked bit of protoplasm, without obviously specialized parts. However, careful study reveals that the organism really consists of a single protoplasmic unit differentiated into cytoplasm and nucleus—it is a cell: an animal.

"But there are no specialized locomotor organs—merely now and again the clear outer layer of protoplasm or ECTOPLASM, flows out, followed by the internal granular ENDOPLASM, so that a projection, or PSEUDOPODIUM, is formed. There is no permanent mouth; food being engulfed by the protoplasm flowing about it as opportunity offers. There is no permanent digestive or excretory apparatus.

"Amoeba, under favorable conditions, grows rapidly and, when it has attained the size limit characteristic of the species, cell division, termed BINARY FISSION, takes place, with the result that from the single large cell there are formed two smaller individuals which soon become complete in all respects. These in turn, grow and repeat the process so that . . . within a few days the original Amoeba has divided its individuality, so to speak,

among a multitude of descendants." (Woodruff, "Animal Biology," pp. 35–36, The Macmillan Company, New York, 1938.) See Protozoa.

Anaerobes. See Aerobes and Anaerobes.

Anions. See Dissociation.

Annelida. See Earthworm.

Appendix, Human. "Near the junction of the large and small intestine in man there is a narrow, blind process, about three and a half inches in length, known as the vermiform appendix. The appendix in man is a vestigial structure and represents the functionless, shriveled, terminal remains of the caecum, the blind beginning of the large intestine. In an herbivorous animal, the caecum is a large, nutritive organ of great importance. In carnivorous animals, the caecum is reduced. The reduction of the terminal portion of the caecum to form an appendix occurs only in man, the anthropoid apes, and some rodents. The frequent pathological condition of the appendix in man has given rise to the aphorism 'that vestigial structures are particularly prone to disease.'" (Ferris, "The Evolution of Earth and Man," Chap. VI, p. 221, Yale University Press, New Haven, Conn., 1929.)

Aristotle. "Aristotle (384–322 B.C.), the most famous pupil of Plato and dissenter from the Platonic School, represents the high-water mark of the Greek students of nature and is justly called the Father of Natural History. Aristotle's contributions to biology are manifold. He took a broad survey of the existing facts and welded them into a science by relying, to a considerable extent, on the direct study of organisms and by insisting that the only true path of advance lay in accurate observation and description. But mere observation without interpretation is not science. Aristotle's generalizations —his elaboration of broad philosophical conceptions of organisms—give to his biological works their perennial significance. Among the facts and supposed facts there are interspersed questions, answers, theories which involve a recognition and remarkable grasp of fundamental biological problems; though of course there are many crudities because adequate apparatus and biological technique were of the distant future. A study of Aristotle's works shows ancient pedigrees for some of the most 'modern' questions of biology, though it is undoubtedly true, as Sachs insists, that one must continually inhibit the tendency to read the present viewpoint into the past, and not assign to earlier writers merits which, if they were alive, they themselves would not claim.

"We have not mentioned a single discovery made by Aristotle—and with purpose. Aristotle's position as the founder of biology rests chiefly on his viewpoint and his methods. Plato relied on intuition as the basis of knowledge. Aristotle emphasized observation and induction, insisting that errors arise not from the false testimony of our sense organs but from false interpretations of the data they afford. 'We must not accept a general principle from logic only, but must prove its application to each fact; for it is in facts that we must seek general principles, and these must always accord with facts from which induction is the pathway to general laws.' But it is not to be

imagined that Aristotle always followed his own advice; few great men do—'no pilot can explore unsurveyed channels without a confidence which sometimes leads to disaster.' It must be admitted that Aristotle frequently lapsed into unbridled speculation which tended to obscure the methods that time has shown produce the most enduring results, though, as Huxley has well said, 'It is a favorite popular delusion that the scientific enquirer is under a sort of moral obligation to abstain from going beyond that generalization of observed facts which is absurdly called 'Baconian' induction. But any one who is practically acquainted with scientific work is aware that those who refuse to go beyond fact, rarely get as far as fact; and any one who has studied the history of science knows that almost every step therein has been made by the 'Anticipation of Nature,' that is, by the invention of hypotheses, which, though verifiable, often had very little foundation to start with; and not infrequently, in spite of a long career of usefulness, turned out to be wholly erroneous in the long run.

"With the Greeks, then, biology emerged from the shadows of the past and took concrete form—a fact which apparently the discerning mind of Aristotle appreciated since, though frequently referring to the ancients, he wrote: 'I found no basis prepared; no models to copy. . . . Mine is the first step, and therefore a small one, though worked out with much thought and hard labor. It must be looked at as a first step and judged with indulgence.'" (Woodruff, "The Development of the Sciences," Chap. VI., pp. 216–218, Yale University Press, New Haven, Conn., 1923.)

Arthropoda. "The great phylum Arthropoda is the largest phylum of the animal kingdom in the number of known species and possibly also in the total number of individuals. Thus the waters of the earth, both fresh and salt, swarm with myriads of Arthropods consisting for the most part of microscopic Crustacea, close relatives of the Crayfish, while the soil and air are dominated, at least in numbers, by an almost infinite variety of Insects which also belong to the Arthropods. In the study of the Crayfish we have seen that to the segmented body, first noted in the Annelida, the Arthropods have added paired, jointed appendages which are highly modified in many instances for the performance of definite functions. Moreover the principles of segmental specialization and cephalization, which were introduced in certain of the Annelida, are further exemplified and firmly established in the Arthropods. It is noteworthy, however, that in the more primitive members of this phylum, as in most of the Annelida, segmental specialization is lacking except in the head segments. Also characteristic of the arthropodan body is a secreted exoskeleton with definite body regions, and with joints provided for flexibility, but requiring molting for growth of the body. Finally a great reduction of the coelom, as compared with the Annelids, is characteristic.

"Commonly, five classes of Arthropods are recognized: (1) the *Crustacea*, represented by the Crayfish, most of which are water-living forms which breathe by gills; (2) the *Arachnoidea*, represented by the Spider, most of which are land-living forms breathing by peculiar book-lungs; (3) the *Onychophora*, a very small class represented by Peripatus—a living link between Annelid

and Arthropod; (4) *Myriapoda*, represented by the Centipedes, with a minimum of segmental and appendage specialization; (5) the *Insecta*, represented by Grasshopper and Honey Bee and, on the whole, exhibiting the acme of invertebrate development." (Baitsell, "Manual of Biology," pp. 208–209, The Macmillan Company, New York, 1936.)

Atoms. See Matter, Dissociation.

Beaumont, William. "William Beaumont (1785–1853), a physician stationed at a military post in the primeval forest of northern Michigan, grasped the unique opportunity of studying the processes of digestion in the victim of a gunshot wound that had caused a permanent gastric fistula. The story of Alexis St. Martin's accident and of Beaumont's wisdom in the management of the case are clearly set forth in Beaumont's own words, which follow. The accident occurred on June 6, 1822. The patient had recovered within a few months, and Beaumont attempted during the next two years, by repeated dressings, to close the wound. The first observations of a physiological nature were begun in May, 1825. Full details of his studies were published in a separate volume in 1833. After giving the case history, Beaumont described briefly the work of his predecessors in the same field and then put down his epoch-making observations upon movements of the stomach during digestion, the normal appearance of the gastric mucous membrane, the fact that gastric juice is secreted only as a result of the taking of food, mechanical irritation being ineffective. By a series of ingenious arguments he concluded that, in addition to free hydrochloric acid, which Prout had previously observed, there was also present in the gastric juice another active chemical substance, to which Schwann in 1835 gave the name of *pepsin*. Beaumont's observations illustrate the enormous contribution that may come from painstaking clinical observation, and those who read his little book must inevitably feel the inspiration of his great example.

"'Whilst stationed at Michillimackinac, Michigan Territory, in 1822, in the military service of the United States, the following case of surgery came under my care and treatment.

"'Alexis St. Martin, who is the subject of these experiments, was a Canadian, of French descent, at the above mentioned time about eighteen years of age, of good constitution, robust and healthy. He had been engaged in the service of the American Fur Company, as a voyageur, and was accidentally wounded by the discharge of a musket, on the 6th of June, 1822. . . . The whole mass of materials forced from the musket, together with fragments of clothing and pieces of fractured ribs, were driven into the muscles and cavity of the chest.

"'I saw him in twenty-five or thirty minutes after the accident occurred, and, on examination, found a portion of the lung, as large as a Turkey's egg, protruding through the external wound, lacerated and burnt; and immediately below this, another protrusion, which, on further examination, proved to be a portion of the stomach, lacerated through all its coats, and pouring out the food he had taken for his breakfast, through an orifice large enough to admit the fore finger.

EXPERIMENT I

"'August 1, 1825. At 12 o'clock M., I introduced through the perforation, into the stomach, the following articles of diet, suspended by a silk string, and fastened at proper distances, so as to pass in without pain—*viz.*:—a piece of high seasoned *a la mode* beef; a piece of raw, salted, fat pork; a piece of raw, salted, lean beef; a piece of boiled, salted beef; a piece of stale bread; and a bunch of raw, sliced cabbage; each piece weighing about two drachms; the lad continuing his usual employment about the house.

"'At 1 o'clock P.M., withdrew and examined them—found the cabbage and bread about half digested: the pieces of meat unchanged. Returned them into the stomach.

"'At 2 o'clock P.M., withdrew them again—found the cabbage, bread, pork, and boiled beef, all cleanly digested, and gone from the string; the other pieces of meat but very little affected. Returned them into the stomach again.

"'At 3 o'clock P.M., examined again—found the *a la mode* beef partly digested: the raw beef was slightly macerated on the surface, but its general texture was firm and entire. The smell and taste of the fluids of the stomach were slightly rancid; and the boy complained of some pain and uneasiness at the breast. Returned them again.

"'The lad complaining of considerable distress and uneasiness at the stomach, general debility and lassitude, with some pain in his head, I withdrew the string, and found the remaining portions of aliment nearly in the same condition as when last examined; the fluid more rancid and sharp. The boy still complaining, I did not return them any more.

"'August 2. The distress at the stomach and pain in the head continuing, accompanied with costiveness, a depressed pulse, dry skin, coated tongue, and numerous white spots, or pustules, resembling coagulated lymph, spread over the inner surface of the stomach, I thought it advisable to give medicine; and, accordingly, dropped into the stomach, through the aperture, half a dozen calomel pills, four or five grains each; which, in about three hours, had a thorough cathartic effect, and removed all the foregoing symptoms, and the diseased appearance of the inner coat of the stomach. The effect of the medicine was the same as when administered in the usual way, by the mouth and oesophagus, except the nausea commonly occasioned by swallowing pills.'" . . . (Fulton, "Selected Readings in the History of Physiology," pp. 164–169, Courtesy of Charles C. Thomas, Springfield, Ill., 1930.)

Binomial Nomenclature. See Taxonomy.

Biogenesis. The term given by Huxley to designate the now generally accepted belief that life comes only from preexisting life, as opposed to the view, firmly established until the middle of the nineteenth century, that protoplasm was continually being formed spontaneously from nonliving matter. The final establishment of biogenesis and the downfall of abiogenesis was due very largely to the researches of Pasteur. "In the two-thirds of a century that have since elapsed, it has been shown in various ways that if due pre-

cautions be taken to exclude living organisms and their eggs, spores, or seeds, no fermentation, putrescence, or other production of minute life ever takes place. It is all a question of the adequacy of the precautions. This adequacy is a question of technique." (Singer, "Story of Living Things," p. 441, Harper & Brothers, New York, 1931.)

Biological Sciences.

Biology, the science of life
- of animals **Zoology**
  - Physiology (chemical and physical processes)
  - Morphology (structure)
    - Anatomy (gross structure)
    - Histology (microscopic structure)
    - Embryology (development of structure, studied partly by physiological method)
  - Cytology (morphology and physiology of cells)
  - Pathology (morbid morphology and physiology)
  - Psychology (mental phenomena, studied largely by physiological method)
  - Ecology (adaptation and other relationships of organism to its environment, studied chiefly by physiological method)
  - Taxonomy (classification, based chiefly on comparative anatomy but partly on physiology)
- of plants **Botany**
  - Physiology
  - Morphology
  - Cytology
  - Pathology
  - Ecology
  - Taxonomy

  Each of these has its physiological aspects as in corresponding zoological studies
- of those microorganisms and other forms, difficult to classify as true plants or true animals,
  - **Bacteriology,** dealing with plant-like microscopic forms,
  - **Mycology,** dealing with fungi,
  - **Protozoology,** dealing with animal-like microscopic forms

  Each of these branches of biology subdivides into physiology, morphology, cytology, pathology, ecology and taxonomy, and each of these subdivisions has its physiological aspects.

(Mitchell, A Textbook of General Physiology, p. xiv, McGraw-Hill Book Company, Inc., New York, 1938.)

Biological Elements. The problem of determining which chemical elements are essential to the activities of living matter is difficult. Certain elements, such as silicon and aluminum, are so widespread in nature that it would be hard for organisms to prevent their entering their cells in small

quantities. Such substances are usually reported in chemical analyses of tissues, including those of man, but there is no evidence that they perform any biological functions in animal protoplasm. Certain other elements, though undoubtedly of great functional importance, exist in such small quantities in organisms that an investigation of their role is extremely difficult. The essential part played by such an element can be determined only by restricting the supply of this element in the environment of a plant or animal and then observing whether or not the restriction has a deleterious effect on the organism. Sometimes natural environments are deficient in particular elements. Thus a restricted iodine supply in certain regions produces endemic goiter in man; a restricted cobalt supply, bush-sickness in sheep; a restricted boron supply, various diseases of fruit trees and edible roots. These diseases can all be easily cured by adding the missing element. Experimental investigations of such deficiencies are very difficult, as it is hard to prepare pure solutions for the growth of plants and far harder to prepare pure solid organic food stuffs, free from the element in question, for the higher animals. At present, information of this sort has been obtained chiefly for green plants; for fungi; and, with considerably less accuracy, for the rat. Apart from such experiments, the probability of the essential role of an element is enhanced by the existence of special organic compounds of the element in the tissues of organisms and of high concentration of the element in the organs.

As a provisional and rough classification, the generally essential biological elements may be classified as:

1. *Universal primary constituents*, occurring in all organisms and constituting more than 1 per cent of the living matter of the earth: oxygen, hydrogen, carbon, nitrogen, phosphorus, sulphur. (In man, more calcium and less sulphur are present than in the organic world as a whole.)

2. *Universal secondary constituents*, occurring in all organisms and constituting between 0.05 and 1.0 per cent of the living matter of the earth: sodium, magnesium, chlorine, potassium, calcium, iron.

3. *Universal microconstituents*, occurring in all organisms adequately studied, and apparently essential to living matter, but present in very minute amounts, less than 0.05 per cent: manganese, copper, zinc, iodine, probably cobalt, and possibly arsenic and fluorine.

4. Elements of probable biological significance in plants or some species of animals, but, as far as is known, having no function in man, though further research may indicate the universal importance of some of them: boron, silicon, vanadium, gallium, selenium, bromine, strontium, molybdenum, barium, and possibly aluminum and scandium.

5. In addition to these 30 elements, the atoms of which appear to be the ultimate building stones from which all organisms are constructed, evidence for the existence of at least 28, and possibly 42, other elements in the bodies of animals or plants has from time to time been obtained, thus making a total of at least 58 and possibly 72 of the 92 elements believed to exist. Most of these, such as the rare earth elements deposited with calcium in bones or the argon dissolved from the air by blood and other body fluids, certainly have no biological function; some others, however, may turn out to be true micro-

constituents. In man, the most constantly present of such accidental elements are lithium, rubidium, nickel, silver, tin, lead, and mercury. Minute quantities of radium occur in organisms, but the commoner, though less soluble, radioactive element, thorium, seems to be absent from biological material.

A few elements exist in nature in quantities deleterious to organisms. Fluorine in water supplies has been found to cause mottled teeth, a serious dental condition common in the Southwestern states. Selenium, which is essential to some species of the small pea-like plant Astragalus, is highly poisonous to most animals. Domestic animals eating the plant become afflicted with "loco disease." Selenium may enter wheat plants from seleniferous soils, derived in part from rocks containing fossil Astragalus; and such wheat is unfit for human consumption. At least one case has been recorded of stock suffering from an overdose of molybdenum naturally accumulating in pasture grasses from a molybdenum-rich soil.

In general, the biological elements are the light and common elements of the universe. In both the universe as a whole and the chemical composition of organisms, the common elements are the elements of low atomic weight. The only important exceptions to the rule of decreasing abundance of elements with increasing atomic weights are the elements lithium, beryllium, and to a less extent, perhaps, boron, which are lighter but much rarer in the universe than carbon and nitrogen. These three elements can be disintegrated into helium and hydrogen in the interiors of stars and so have tended to disappear from the universe. It is therefore very interesting to find that lithium and beryllium are the only light elements for which no indication of any biological function has ever been found. Boron, however, which is important to plants, is abnormally available at the earth's surface, owing to the great solubility of the borates, and so has entered into the living world.

The following table indicates the order of abundance of the commoner elements in the universe as a whole, in the earth's crust, in sea water, in the atmosphere, and in the human body.

Universe as a whole	Earth's crust	Sea water	Atmosphere	Human body
Hydrogen	Oxygen, 49.5 %	Oxygen, 84.2 %	Nitrogen, 78 %	Oxygen, 65 %
Helium	Silicon, 25.7 %	Hydrogen, 12.0 %	Oxygen, 21 %	Carbon, 18.3 %
Oxygen	Aluminum, 7.5 %	Chlorine, 2.1 %	Argon, 1.0 %	Hydrogen, 10 %
Carbon	Iron, 4.7 %	Sodium, 1.2 %	Hydrogen, *ca.*0.1 %	Nitrogen, 2.65 %
Nitrogen	Calcium, 3.4 %	Magnesium, 0.14 %	Carbon, *ca.*0.01 %	Calcium, 1.4 %
Neon	Sodium, 2.6 %	Sulphur, 0.097 %	Other constituents, less than 0.01 %	Phosphorus 0.8 %
Iron	Potassium, 2.4 %	Calcium, 0.046 %		Potassium, 0.3 %
Silicon	Magnesium, 2.0 %	Potassium, 0.041 %		Sodium, 0.3 %
Magnesium	Hydrogen, 1.0 %	Carbon, 0.016 %		Chlorine, 0.3 %
Argon	Titanium, 0.5 %	Other constituents, less than 0.01 %		Sulphur, 0.2 %
Nickel	Carbon, 0.4 %			Magnesium, 0.04 %
Aluminum	Chlorine, 0.2 %			Iron, 0.04 %
Calcium	Sulphur, 0.15 %			Other constituents, less than 0.04 %
Sodium	Manganese, 0.1 %			
Other constituents probably less than 0.01 %	Phosphorus, 0.1 %			
	Other constituents, less than 0.1 %			

Owing to the fact that it is difficult to estimate the relative amounts of hydrogen and helium in the universe, though it is known that these are the two commonest elements, no percentages are given for the first column. The 14 elements given in that column, however, are probably the only ones that constitute at least 0.01 per cent of the universe. Except for the presence of large amounts of the inert gases, helium and neon, the composition of man is not unlike that of the average inorganic matter of the universe; more like the average, in fact, than are the earth's crust, the sea, or the air. In both the universe and in living organisms, hydrogen, oxygen, carbon, and nitrogen are the chief active elements existing in large amounts and in more or less comparable proportions.

The importance of the distribution of elements is best seen if we compare the composition of a unit volume, say, 1,000 cc. of sea water with an equal volume of living organisms, say, fish. The marine animal has had no difficulty in obtaining its hydrogen, oxygen, chlorine, sulphur, magnesium, or sodium; its calcium content will be from five to ten times that of the sea water; its carbon content and content of microconstituents, about one thousand times; its combined nitrogen, phosphorus, and iron contents, about ten thousand times. These last three elements, then, ultimately set a limit to the amount of life in the sea and so to the number of fish available for human consumption. This aspect of the biological elements is of great importance in the study of biogeochemistry, the science that considers the transformations of chemical substances through organisms in nature. (Hutchinson, Osborn Zoological Laboratory, Yale University, New Haven, Conn., January, 1940.)

Biology and Medicine. "Before leaving the Greeks we must mention Hippocrates (460–370 B.C.), the Father of Medicine. Writing a generation before Aristotle, at the height of the Age of Pericles, Hippocrates crystallized the knowledge of medicine into a science, dissociated it from philosophy, and gave to physicians 'the highest moral inspiration they have.' 'To him medicine owes the art of clinical inspection and observation, and he is, above all, the exemplar of that flexible, critical, well-poised attitude of mind, ever on the lookout for sources of error, which is the very essence of the scientific spirit. . . . The revival of the Hippocratic methods in the seventeenth century and their triumphant vindication by the concerted scientific movement of the nineteenth, is the whole history of internal medicine.'

"Medicine, the most important aspect of applied biology, is the foster parent of zoology and botany, since a large proportion of biological advances have been the work of physicians. Until relatively recently the schools of medicine afforded the only training, and the practice of medicine the chief livelihood for men especially interested in general biological problems. The history of medicine and of biology as a so-called pure science are so inextricably interwoven that the consideration of one involves that of the other. Indeed, the physicians form the only bond of continuity in biological history between Greece and Rome. The chief interest of the Romans lay in technology, and therefore it is natural that the practical advantages to be gained

should ensure the advance of medicine. As it happens, however, two Greek physicians were destined to have the most influence: Dioscorides (c. 64 A.D.), an army surgeon under Nero, and Galen (131–201 A.D.), physician to the Emperor Marcus Aurelius and his son, Commodus.

"Just as Theophrastus established botany as a pure science, so Dioscorides was the originator of the pharmacopoeia, writing, as he did, not only a work which was the first one on medical botany, but one which, gaining authority with age, was the sole standard 'botany' for fifteen centuries. Theophrastus was long overshadowed. Most of the botanical writings up to the seventeenth century were annotations on the text of Dioscorides.

"Galen was the most famous physician of the Roman Empire and his voluminous works represent both the depository for the anatomical and physiological knowledge of his predecessors, rectified and worked over into a system, and a large amount of original investigation. Galen was a practical anatomist who described from dissections and insisted on the importance of vivisection and experiment, and therefore he may be considered the first experimental physiologist and the founder of experimental medicine. Galen gave to medicine its standard anatomy and physiology for fifteen centuries.

"Any consideration of the biological science of Rome would be incomplete without a reference to the vast compilation of a fact and fiction, indiscriminately mingled, made by Pliny the Elder (23–79). It was beside the path of biological advance, but long the recognized 'Natural History,' passing through some eighty editions after the invention of printing. Its prestige was largely due to the fact that it was written in Latin, whereas the great works on biological subjects were in Greek.

"For all practical purposes we may consider that biology at the decline of the Roman Empire was represented in the works of Aristotle, Theophrastus, Dioscorides, Galen, and Pliny. Even these exerted little influence during the Middle Ages, being saved from total loss for future generations chiefly by Arabian scientists, and in the monasteries of Italy and Britain. We cannot pause to consider the various causes which resulted in the almost complete break in the continuity of learning in general and science in particular during the dormant period in western Europe. Suffice it to say that contributing factors were wars and rumors of wars, the destruction of the libraries of Alexandria, the antagonism of Christian and pagan ideals, and the emphasis by the Church, which held the gates of learning, of the written word in place of observation of nature as it is. To a very large extent 'truth and science came to mean simply that which was written, and inquiry became mere interpretation,' though recent historical studies are revealing medieval scientific manuscripts which may necessitate a reappraisal of the period.

"In so far as science reached the people in general, it was almost solely from small compilations of corrupt texts of ancient authors interspersed with anecdotes and fables. Quite characteristic of the times is the oft-quoted *Physiologus*, found in many forms and languages, that evolved into a collection

of natural history stories in which the centaur and phoenix take their place with the frog and crow in affording allegorical illustrations of texts and in pointing out more or less evident morals. The line of demarcation between the *Physiologus* and the *Bestiaries* is ill defined, while the remnants of the latter are incorporated in the early works of the Renaissance encyclopaedists.

"The scientific Renaissance may be said to owe its origin to the revival of classical learning and to the translation and study of the writings of Aristotle and others which had been under eclipse for a thousand years. These were so superior to the existing science that, in accord with the spirit of the time, Aristotle and Galen became the bible of biology. The first works were merely commentaries on the classical authors, but as time went on more and more new observations were interspersed with the old until elaborate and voluminous treatises describing all known forms of plants and animals were produced. In short, the climax of the scientific Renaissance involved a turning away from the authority of Aristotle and an adoption of the Aristotelian method of observation and induction." . . . (Woodruff, "The Development of the Sciences," Chap. VI, pp. 218–221, Yale University Press, New Haven, Conn., 1923.)

Blood Pressure. Stephen Hales (1677–1761) took the next important step after Harvey and Malpighi in elucidating the physiology of the circulation. The determination of blood pressure made it possible to calculate the work done by the heart, and to estimate for the first time the magnitude of the peripheral resistance. The following selection is taken from his "Haemastaticks," published in 1733. (Spelling modernized.)

"1. In December I laid a common field gate on the ground, with some straw upon it, on which a white mare was cast on her right side, and in that posture bound fast to the gate; she was fourteen hands and three inches high; lean, tho' not to a great degree, and about ten or twelve years old. This and the above mentioned horse and mare were to have been killed, as being unfit for service.

"2. Then laying open the left jugular vein, I fixed to that part of it which comes from the head, a glass tube, which was four feet, and two inches long.

"3. The blood rose in it, in three or four seconds of time, about a foot, and then was stationary for two or three seconds; then in three or four seconds more, it rose sometimes gradually, and sometimes with an unequally accelerated motion nine inches more, on small strainings of the mare: Then upon greater strainings it rose about a yard, and would subside five or six inches: Then upon a larger strain or struggle of the mare, it rose so high, as to flow a little out at the top of the tube; so that had the tube been a few inches higher, it would have risen probably to that height.

"4. When the mare ceased to strain and struggle, the blood subsided about eighteen or twenty inches; so the return of the blood into the vein was not hindered by the valves; which I have also observed in other parts where there are valves, tho' sometimes they absolutely hinder the return of any fluid.

"5. The diameter of the brass pipe and tube which were fixed to the vein, were nearly one seventh of an inch: The diameter of the jugular vein about half an inch.

"6. Then laying bare the left carotid artery, I fixed to it towards the heart the brass pipe, and to that the wind-pipe of a goose; to the other end of which a glass tube was fixed, which was twelve feet nine inches long. The design of using the wind-pipe was by its pliancy to prevent the inconveniencies that might happen when the mare struggled; if the tube had been immediately fixed to the artery, without the intervention of this pliant pipe.

"7. There had been lost before the tube was fixed to the artery, about seventy cubic inches of blood. The blood rose in the tube in the same manner as in the case of the two former horses, till it reached to nine feet six inches height. I then took away the tube from the artery, and let out by measure sixty cubic inches of blood, and then immediately replaced the tube to see how high the blood would rise in it after each evacuation; this was repeated several times, till the mare expired, as follows, viz.

"8. We may observe, that these three horses all expired, when the perpendicular height of the blood in the tube was about two feet.

"9. These 833 cubic inches of blood weigh 28.89 pounds, and are equal to fourteen wine quarts, the large veins in the body of the mare were full of blood, there was some also in the descending aorta, and in both ventricles and auricles." (Fulton, "Selected Readings in the History of Physiology," pp. 58–60, Charles C. Thomas, Springfield, Ill., 1930.)

Brownian Movement. "In 1827, a British botanist, Robert Brown, observed that microscopically small particles of pollen dust, when suspended in water, are in a state of constant agitation. They move incessantly in a random, zigzag manner. The smaller the particles are the greater is the activity. Now it can be shown that the Brownian movement, quantitatively as well as qualitatively, is just what we should expect on the basis of the kinetic molecular theory of matter. The suspended particle is being constantly bombarded from all sides by the moving molecules of the liquid. If the particle is so large as to be visible to the unaided eye, no motion will be perceptible, since the number of molecular blows to which the particle is subjected at any given moment is so large that they practically balance one another. However, if the suspended particle is very minute, such an equalization of impacts is not likely to occur, the less so the smaller the particle. In response to this unequal bombardment, greater now on one side, now on another, the particle darts about in a zigzag course, thus revealing to us the movement of the molecules of the liquid surrounding it." (Watkeys, "An Orientation in Science," Chap. III, p. 137, McGraw-Hill Book Company, Inc., New York, 1938.)

Buffon. See Organic Evolution.

Calorie. "In order to be able to discuss energy relationships intelligently we need to have some means of designating definite amounts. The form of energy into which all other forms tend to convert themselves is, as we have

seen, heat. A convenient energy unit, then, is the heat unit. The amount of heat required to raise the temperature of 1 gram (1/28 oz.) of water 1 degree centigrade (strictly from 14° to 15°) is taken as the unit. This is known as the *gram calorie*. For convenience when large amounts of heat are involved a second unit just one thousand times as great is also used. This is called the *kilocalorie* or simply the *Calorie*, usually distinguished from the gram calorie by the use of the capital initial. Although the calorie is strictly a heat unit it serves as an expression for any form of energy. If we speak of any engine as able to furnish a certain number of calories we mean that if all the energy were to appear as heat that many calories would be liberated. As a matter of fact much of the energy may actually take other forms, as it does in the case of the contracting muscle." (Martin, "The Human Body," p. 103, Henry Holt & Company, New York, 1935.)

Carbohydrates. See Cellulose, Glucose, Lactose, Starch, Sucrose.

Cellulose. "Cellulose chemists recognize not one substance that is cellulose but a group of substances, the celluloses. Modern research has produced an alpha cellulose that is as near a chemical entity as any cellulose heretofore attained; but although this may be regarded as a definite cellulose, there are others. The naturally occurring celluloses are of three groups: the true, the compound, and the hemi- or reserve celluloses. Among the first, that of the cotton fiber is the purest, being 90 per cent true cellulose. Compound celluloses are true celluloses impregnated with other substances. The hemicelluloses are incompletely developed forms of cellulose and other carbohydrate materials such as araban and xylan. In spite of this apparent variety, it does not appear that the celluloses of the various seed-bearing plants are actually different chemical substances; that is, although physical differences (for example, fiber length) exist, and chemical differences in the constitution of the cellulose of the original wood may exist, the residues, termed *cellulose*, obtained from different woods are probably identical in chemical structure.

"Protoplasm, as it builds the plant-cell wall, simultaneously or subsequently secretes substances that occur either as distinct layers alternating with the cellulose or, more usually, as an impregnation of it. Such substances are lignin, suberin, pectin, and cutin. Old wood is lignified cellulose, and cork is suberized cellulose. Pectin may form distinct layers in the cell wall alternating with cellulose, or it may be separately deposited. In general, pectin compounds impregnate the wall, forming so-called pectocelluloses. Cutin is often a surface deposit and occurs as the waxy coating on glossy leaves and fruits. To be superficially deposited, it must pass through the cellulose wall and in so doing adds to the chemical complex that we call *natural cellulose*.

"The hemi- or reserve celluloses constitute an interesting group which differs structurally from the fibrous celluloses. They are more readily hydrolyzed than the true celluloses and break down into sugars (galactose and pentose) of which they are regarded as the anhydrides and from which they receive their names (galactosans and pentosans).

"Associated with cellulose, in a manner similar to that just described for pectin, are numerous other compounds generally regarded, like the hemi-

celluloses, as derivatives of cellulose. Among them are the gums, mucilages, and gelatinous substances, usually produced during heartwood formation. Their origin and chemical constitution are not well understood.

"Cellulose is almost wholly a plant product, yet, like most features used to distinguish plants from animals, it is not an infallible criterion of what is a plant and what an animal. Tunicates and insects are reported to have tunicin in their tests or pellicles. This substance is said to be identical with cellulose.

"Although cellulose is used primarily by the plant as a material for wall building, it may serve, probably in some modified form, as a reserve food. Cellulose is also food for certain animals which, though lacking the capacity to digest it themselves, are nevertheless able to use it because of their intestinal flora. There is no digestive enzyme in the fermentation fluids of higher animals that will act upon cellulose, nor indeed is any intestinal ferment known that will attack the hemicelluloses, the pentosans, or the galactans, yet these last two carbohydrates certainly, and probably some of the higher celluloses, not only are utilized by animals but form an important part of the dietary of herbivora. This is possible because the digestion of the cellulose is carried out by microorganisms. It is said that the intestinal juices of the horse dissolve 70 per cent of favorable nonlignified cellulose but that the ferments are produced by bacteria or Protozoa. The cow is another example of a higher animal that digests cellulose. In all such cases, the fermentation is done by microorganisms. The digestion products apparently are not monosaccharides, as one would expect, but carbon dioxide, methane, and fatty acids, the last only being suitable for nutrition.

"The classical example of the wood-feeding habit in animals is that of termites. Intestinal Protozoa make it possible for these insects to live on wood. When defaunated (robbed of their protozoan companions) by heat or oxygen, they cannot digest wood and die from starvation when fed it, but they can then live on rotted wood, that is to say, wood predigested by fungi. If intestinal Protozoa of the same kind as were removed are returned to the termites, they can again transform wood. This experiment, done by Cleveland, led to the further conclusion that wood-ingesting Protozoa form glycogen by splitting the cellulose into cellobiose and decomposing this, in turn, to glucose, from which they build up glycogen." (Seifriz, "Protoplasm," pp. 459–460, McGraw-Hill Book Company, Inc., New York, 1936.)

Chemical Equations. "By the use of symbols and formulae, it is possible to express concisely chemical changes in the form of chemical equations. For example, the combination of hydrogen with oxygen to form water is expressed as follows:

$$2H_2 + O_2 = 2H_2O$$

"In terms of our theoretical conception of matter, the equation states that two molecules of hydrogen, each consisting of two atoms, react with one molecule of oxygen, consisting of two atoms, to form two molecules of water, each of which is composed of two hydrogen atoms and one oxygen atom. In

agreement with the law of the conservation of mass, the number of atoms of each element on the right-hand side of the equation is the same as that on the left; in other words, the equation is balanced.

"Five types of chemical reactions can be distinguished.

1. The combination of two or more substances to form a more complex substance.

C	+	O_2	=	CO_2
carbon		oxygen		carbon dioxide
$2Mg$	+	O_2	=	$2MgO$
magnesium		oxygen		magnesium oxide

2. The decomposition of a more complex substance into two or more simpler substances.

$2HgO$	=	$2Hg$	+	O_2
mercuric oxide		mercury		oxygen
$2H_2O$	=	$2H_2$	+	O_2
water		hydrogen		oxygen

3. The replacement of an element in a compound by another element.

Mg	+	$2HCl$	=	H_2	+	$MgCl_2$
magnesium		hydrochloric acid		hydrogen		magnesium chloride

4. The double decomposition of two compounds resulting in the formation of two new compounds.

MgO	+	$2HCl$	=	H_2O	+	$MgCl_2$
magnesium oxide		hydrochloric acid		water		magnesium chloride

5. *Molecular Rearrangement.* This kind of chemical change consists in the transformation of one compound into another compound having the same molecular composition but a different arrangement of the atoms within the molecule. The illustration of this phenomenon would involve the introduction of more complicated formulae than those which we have been considering." (Watkeys and Associates, "An Orientation in Science," pp. 150–151, McGraw-Hill Book Company, Inc., New York, 1938.)

Chloride Shift. The transportation of carbon dioxide in the blood stream is a difficult problem. Apparently one of the important factors in this process is a shift in either direction of the chloride ions between the red cells and the blood plasma, the direction of the shift depending upon the amount of carbon dioxide present. Thus in the lungs, when the carbon dioxide is released, the chloride ions leave the red cells and combine with the sodium, which has been in combination with potassium in the plasma, to form sodium chloride. In the tissues, when carbon dioxide is received into the blood, it combines at once

with water in the plasma to form carbonic acid. The latter has the power to displace the chloride from the sodium chloride. The chloride ions now enter the red cells and combine with potassium, which is released as the oxyhemoglobin changes to the less acid hemoglobin, and the potassium chloride (KCl) thus formed remains until the lungs are reached, when the chloride is again released to the plasma in correspondence with the increased acidity of the oxyhemoglobin and its ability to combine with the potassium in the red cells.

Chlorophyll. "Chemists from the time of Berzelius (1839) have struggled with the chemistry of chlorophyll. Willstätter made the first great advance in the determination of the structure of chlorophyll. During the past ten years, Conant, Hans Fischer, Stoll, and Inman, to mention only a few of the workers, have advanced our knowledge of the structure of chlorophyll, and the actual synthesis of the chlorophyll molecule appears imminent.

"Chlorophyll probably exists in the colloidal state in plants, or at least adsorbed upon colloids. It can be extracted with certain organic solvents. The earlier workers thought that various plants were characterized by different varieties of chlorophyll. Willstätter showed, however, that there is only one variety. This exists, at least as isolated in the laboratory, in two forms which have been designated chlorophyll-*a* and chlorophyll-*b*.

"Chlorophyll, possessing the same properties, may be prepared from either fresh or dried leaves. One kilo of fresh leaves gives a yield of 0.9 to 2.1 grams; dried leaves yield 5 to 10 grams. The most suitable solvent for extraction is acetone (80 per cent) for dried leaves, and pure acetone for fresh leaves, sufficient acetone being added so that, allowing for the moisture in the fresh leaves, the resulting solution is 80 per cent acetone. Chlorophyll can be now isolated as readily as can any alkaloid or any sugar, and within a few hours a kilo of dried leaves should yield about 6.5 grams of practically pure chlorophyll.

"Chlorophyll is a bluish-black substance with a strong metallic luster, powdering to a greenish- or bluish-black powder. It has no definite melting point, ranging from 93° to 106°C. for various samples, and is soluble in absolute alcohol to a blue-green solution. It shows neither acidic nor basic properties. Acids change its color to olive brown and split off magnesium which is associated with the molecule." (Gortner, "Outlines of Biochemistry," pp. 732–733, John Wiley & Sons, Inc., New York, 1938. Reprinted by permission.)

Cholecystokinin. "During digestion, bile is needed in the intestine. The sphincter of Oddi relaxes, and peristaltic waves pass over the duodenum milking the bile in the common duct into the duodenum. The major factor in emptying the contents of the gallbladder into the duodenum is a hormone, cholecystokinin, that is liberated from the duodenal mucosa when acid enters the intestine. The discharge of acid chyme from the stomach sets this hormone free, and it is absorbed into the blood stream; some of it reaches the gallbladder, where it causes a contraction of the smooth muscle in the gallbladder wall. There is not very much muscle in the gallbladder, and the contractions are not vigorous but slow and continuous so that the bile is very gradually expelled during the process of digestion. Cholecystokinin is also very effectively liberated from the intestinal mucosa by the presence of fat."

(Crandall, "An Introduction to Human Physiology," p. 159, Courtesy of W. B. Saunders Company, Philadelphia, 1934.)

Cholesterol. See Sterols.

Chondriosomes. "These bodies, or their products, are among the most characteristic of the formed components of the cytosome and are known to occur in nearly all kinds of cells, among both plants and animals, and everywhere showing the same general characters. They have attracted much attention in recent years because of the questions raised by Altmann, Benda, Meves, and their followers concerning their possible significance in histogenesis and heredity; but opinion concerning them is still in a very unsettled state. Morphologically they appear in the form of small granules (*mitochondria*), rods or filaments (*chondrioconts*) and other bodies. . . . More recent studies have shown that they consist of a specific material showing definite cytological and microchemical characters but morphologically highly plastic, so that it may appear under many forms, which are probably to be regarded as only different phases of the same material. The most common of these are separate mitochondria and chondrioconts, both of which may often be observed in the same cell; and all gradations between them may be observed in sections. . . .

"The physico-chemical nature of chondriosomes has been the object of numerous researches. . . . They are soluble in various degrees in dilute acetic acid, ether, acetone, alcohol and other fat-solvents; hence the fact that they are often imperfectly fixed or even destroyed by many of the ordinary fixing agents containing acetic acid, and were often overlooked until a more appropriate technique had been devised." (Wilson, "The Cell in Development and Heredity," pp. 45–47, The Macmillan Company, New York, 1925.)

Classification. See Taxonomy.

Coelenterata. "The phylum Coelenterata, to which Hydra and Obelia belong, includes a wide variety of relatively simple Metozoa, almost all of which are marine in habitat. Three classes are generally recognized, namely: (1) the Hydrozoa, represented by the independent polyp type, like Hydra, and the colonial type consisting of many attached, dependent polyps, as in Obelia; (2) the Scyphozoa, represented by many species of large jellyfishes; and (3) the Actinozoa, represented by an independent polyp type, like the Sea-anemone and the important 'island-building,' colonial Corals, in all of which a considerably greater cellular specialization is exhibited than in Hydra. Throughout these three classes of Coelenterates, basic structural likeness is evident in the body plan of the individuals, which is always diploblastic and radially symmetrical. The enteric cavity is a sac-like structure with one opening for ingestion and egestion, and is encircled by tentacles. All species possess stinging cells (nematocysts). Finally, an alternation of generations, well-shown in Obelia, but subject to great variation, is often found." (Baitsell, "Manual of Biology," pp. 175, The Macmillan Company, New York, 1936.) See Hydra.

Coelom. The body cavity of the triploblastic animals. It is formed originally in the embryo as a result of the splitting of the mesoderm into an

outer layer, which is associated with the body wall, and an inner layer, which forms the wall of the alimentary canal. The cavity developed between the two mesoderm layers is the coelom. In man, the coelom is divided into three portions: namely, the pericardial cavity, or sac, in which the heart lies; the thoracic cavity containing the lungs and heart; and the abdominal, or peritoneal, cavity with various important abdominal organs. The thoracic and abdominal cavities are separated by the diaphragm. Strictly speaking, none of the visceral organs lie in the coelom proper but rather in the cavity formed between the two layers of the serous membranes that cover them. See Serous Membranes.

Colloids. "Matter is said to be in the *colloidal state* when it is permanently dispersed and so finely divided that the individual particles, though larger than molecules, cannot be seen. The water of the Mississippi River is forever muddy because the clay particles contained in it are so small that they do not settle until they meet the salts of the sea, when they quickly fall and form the Mississippi delta. Both the suspension of the finely divided clay particles in the river water and their precipitation by the salts of the sea are colloidal phenomena. A threatening cloud is made up of droplets of water finely dispersed and in relatively permanent suspension in the air; the water is in the colloidal state. When the droplets, through coalescence, become too large, they fall as rain. The tails of comets consist of particles so small that when our earth sweeps through them we see nothing of them, yet illuminated against the black background of the night sky they become brilliant. The cosmic particles of the comet's tail are in the colloidal state, and their luminosity is due to the *scattering* of light, a colloidal phenomenon. The blue color of tobacco smoke or pale forest-fire smoke, of mist, blue eyes, feathers, and skimmed milk is due to the presence of tiny particles in permanent suspension, in other words, to matter in the colloidal state. Metals may be so finely dispersed in water as to remain in permanent suspension. Gold so dispersed forms a classical colloidal suspension. Where dispersed particles settle, as does sand in water, or rise, as does cream in milk, the system is a coarse suspension. Only the smaller particles which remain behind in permanent suspension are colloidal. Minuteness in size of particles and relative permanency in suspension characterize the colloidal state.

"The medium in which the particles of a colloidal system are scattered is termed the *dispersion medium*, or *continuous phase;* and the scattered particles are the *dispersed*, or *discontinuous phase;* thus, the air of clouds is the dispersion medium, and the droplets of water are the dispersed phase.

"Matter finely divided and in permanent suspension is said to be colloidally dispersed rather than in solution, because the particles are above the molecule in size, though one may speak of colloidal solutions; furthermore, a molecular dispersion may be colloidal if the molecules are exceedingly large, as in the case of proteins.

"As particle size is characteristic of the colloidal state, the latter may be (somewhat arbitrarily) defined in terms of the former. The maximum size of colloidal particles is conveniently placed at the limit of microscopic

visibility. The minimum size is above that of the average molecule. This means that the largest colloidal particles are below 0.1 u or 0.0001 mm. in diameter and therefore invisible and above 1 mμ or 0.000001 mm." (Seifriz, "Protoplasm," pp. 88–89, McGraw-Hill Book Company, Inc., New York, 1936.) See Measurements; Energy.

Comparative Anatomy. "The first step towards scientific classification was made . . . by Aristotle in emphasizing anatomical characters as taxonomic criteria, so that to all intents and purposes classification implies comparison of structural details. Indeed, Aristotle recognized the unity of structural plan throughout the chief animal groups, and in reference to man he says, 'whatever parts a man has before, a quadruped has beneath; those that are behind in man form the quadruped's back.' Not only did he appreciate homology, but also correlation of parts and division of labor in the economy of the animal body. And Theophrastus approached plant morphology in the same philosophical spirit. . . . But it probably would be reading too much into the past to assign the origin of comparative anatomy of animals in the modern sense of the term to Greek, Roman, or early Renaissance science, since description rather than comparison was the keynote. The same may be said of the anatomical work of Vesalius, Harvey, and Malpighi, though the latter compared the microscopic structure of various organs, and in his *Anatomy of Plants*, which shares with Grew's *Anatomy* the honor of founding vegetable histology, emphasized the importance of the comparative method. Owing to the less marked structural differentiation of plants in comparison with animals, plant anatomy does not lend itself so readily to descriptive analysis and therefore an epoch in the study of comparative anatomy is less defined in botany than in the sister science. Accordingly both reason and expediency warrant confining our attention to the comparative anatomy of animals.

"Probably the first consistent attempt to make a comparative study of the form and arrangements of the parts of animals is represented in a volume published in 1645 by Severinus (1580–1656) of Naples, in which he concluded that many vertebrates are constructed on the same plan as man, though Belon, nearly a century earlier, figured and compared the skeletons of bird and man side by side in the same posture, and as nearly as possible bone for bone. Tyson (1650–1708) of Cambridge at the end of the seventeenth century definitely instituted the monographic treatment of comparative morphological problems in his study of the anatomy of man and monkeys.

"Comparative anatomy, however, as a really important aspect of biological work, in fact as a science in itself, was the result of the life work of Cuvier (1769–1832) of Paris during the first quarter of the last century. It is true that his immediate predecessors, such as John Hunter (1728–1793), the founder of the Hunterian Collection, the nucleus of the Anatomical Museum of the Royal College of Surgeons in London, Camper (1722–1789) of Groningen and Vicq d'Azyr (1748–1794) of Paris, added synthesis to analysis and reached a broader viewpoint in anatomical study, but Cuvier's claim to fame rests on the remarkable breadth of his investigations—his grasp of the comparative

anatomy of the whole series of animal forms. And not content merely with the living, he made himself the first real master of the anatomy of fossil vertebrates and as such is the founder of vertebrate paleontology, while his contemporary, Lamarck, holds the same relation to invertebrate paleontology.

"Cuvier's position in the history of anatomy is largely due to his emphasizing, as Aristotle had done before him, the functional unity of organisms—that the interdependence of organs results from the interdependence of function and that structure and function are two aspects of the living machine which go hand in hand. Cuvier's famous principle of correlation—'Give me a tooth,' said he, 'and I will construct the whole animal'—is really an outcome of this viewpoint. Every change of function involves a change in structure and therefore, given extensive knowledge of function and of the interdependence of function and structure, it is possible to infer from the form of one organ that of most of the other organs of an animal. 'In a word, the form of the tooth implies the form of the condyle; that of the shoulder blade that of the claws, just as the equation of a curve implies all its properties.'

"Although Cuvier undoubtedly allowed himself to exaggerate his guiding principle until it exceeded the bounds of facts, he was above all in his science and philosophy a hard-headed conservative and autocrat. He opposed with equal vigor the influence of the *Naturphilosophie* of Schelling and his school with its transcendental anatomy, Platonic archetypes, and the like, as well as the evolutionary speculations of Lamarck and his school. From the vantage points of today we know that in one case he was right and in the other wrong—though, in so far as the facts then available, his opposition was justified in both cases.

"Cuvier's immediate successors in France were Milne-Edwards (1800–1885) and Lacaze-Duthiers (1821–1901); in Germany, Meckel (1781–1833), Rathke (1793–1860), Müller, and Gegenbaur (1826–1903); in England, Owen and Huxley, and in America, Agassiz (1807–1873); Cope (1840–1897), and Marsh (1831–1899). Among these, Owen (1804–1892) perhaps demands special mention. At once a peculiar combination of Cuverian obstinacy in regard to facts and of transcendental imagination, Owen spent a long life dissecting with untiring patience and skill a remarkable series of animal types, as well as in reconstructing extinct forms from fossil remains. Aside from the facts accumulated, probably his greatest contribution was making concrete the distinction between homologous and analogous structures, which has been of the first importance in working out the pedigrees of plants as well as animals—though Owen himself took an enigmatical position in regard to organic evolution." (Woodruff, "The Development of the Sciences," Chap. VI, pp. 233–236, Yale University Press, New Haven, 1923.)

Complement Fixation. The complement-fixation tests, such as the Wassermann test, have long since become highly standardized and a matter of routine in laboratories and hospitals throughout the world. Such tests require solutions of complement and antigen with measured content and with the antigen made specifically for the disease in question. It is necessary to keep in mind certain characteristics that serve to differentiate between comple-

ment and lysin. Thus: (1) Complement is not specific for a particular lysin but reacts whenever any lysin is present together with antigen; (2) it is easily destroyed by heating; (3) it may be standardized by the proper laboratory methods, and the necessary amount supplied to react with a determined amount of antigen.

Lysin, on the other hand, (1) is specific against a particular invader. Consequently, a lytic antibody is never present in the blood unless the tissues have been invaded by foreign material; (2) it is not easily destroyed by heating. Therefore, by heating blood serum, the normal complement will be destroyed, while the lysin remains.

With the antigen and complement standardized and of known strength, the only unknown factor in the test is the presence of lysin in the serum obtained from the patient, and that is what the test aims to determine. The components of a complement-fixation test may be outlined as follows:

A. Standardized complement in solution.

B. Standardized solution of antigen for the specific disease, in sufficient amount to combine with the complement, provided lysin is present.

C. Blood serum from patient, which has been heated to destroy the complement normally present, but which will contain the lysin if the patient has the disease.

When these substances *A*, *B*, and *C* are combined under the proper conditions in a test tube, there are two possibilities:

1. No reaction will occur if the serum *C* is free from lysin.

2. Reaction will occur if lysin is present, and the complement will be bound or fixed (complement-fixation); that is, complement *A* and lysin *C* will combine to destroy antigen *B* just as in the body.

It is impossible to tell from the appearance of the liquid in the test tube as to whether or not a reaction has occurred, but the answer will be given by the introduction of the hemolytic system as a visible indicator. It will be necessary to add two additional substances to those previously combined (*A*, *B*, *C*), namely;

D. Blood serum from a rabbit containing a hemolysin against red blood cells of the sheep. This hemolysin has been previously developed in the rabbit in response to repeated injections of sheep corpuscles. It is strong enough to cause the hemolysis of these corpuscles when complement is present. The rabbit serum has been heated to destroy all complement normally present.

E. Finally, the red blood cells of the sheep are added as the hemolytic antigen.

With this very ingenious hemolytic indicator it will be possible to secure visible evidence in a short time as to whether or not the patient has the disease. For, if the disease is present, a reaction will previously have occurred between *A*, *B*, and *C*, as stated in (2) above, and the complement will have been used. In this case, the addition of the hemolytic rabbit serum *D* and the sheep blood cell antigen *E* will cause no further reaction, since there will be no complement. Accordingly, the red cells will remain intact at the bottom of the tube with a clear liquid above.

If, however, the patient is free from the disease, a further reaction will occur when the two substances D, E, associated with the hemolytic system are added, for unbound complement A will be present to react with the hemolytic antibody D and antigen E. It will be remembered that complement is not specific for a particular antibody, and consequently it will react whenever any lysin and antigen are present. The reaction in this instance will cause the disruption of the sheep corpuscles (antigen) and the release of the hemoglobin into the solution which will gradually be uniformly colored as the hemoglobin diffuses throughout, as indicated in the following equation:

$$\text{Complement } A + \text{rabbit hemolysin } D + \text{sheep red cells antigen } E = \text{hemolysis}$$

A highly colored red solution, with no intact corpuscles at the bottom of the tube, indicates complete freedom from the disease, that is, a negative test. On the contrary, a transparent solution with no corpuscles destroyed indicates a severe active infection (+4). Less severe infections are indicated by a corresponding increase in hemolysis and are commonly designated +3, +2, and +1.

Cranial Nerves, Human. I. *Olfactory.* The first pair of cranial nerves has its origin in the forebrain. Only sensory fibers are present in this pair which innervate the olfactory cells in restricted areas of the nasal epithelium.

II. *Optic.* These nerves contain only sensory fibers that innervate the retina and thus receive the impulses from the visual cells. They have their origin in the midbrain. Emerging from the brain stem, the optic nerves form the optic chiasma on the ventral surface of the midbrain and then continue to each eye.

III. *Oculomotor.* As the name indicates, this pair of nerves innervates certain eye muscles concerned with movements of the eyeball. They are concerned also with lens accommodation and pupillary changes. In addition, sensory fibers are present that carry afferent impulses from the eye muscles. The oculomotor nerves have their origin in the anterior portion of the hindbrain.

IV. *Trochlear.* These nerves consist largely of motor fibers which, in conjunction with fibers from III and VI, innervate certain eye muscles. Sensory fibers possibly present carrying impulses from the eye muscles. They emerge from the hindbrain but extend anteriorly for a distance before reaching the eyes.

V. *Trigeminal.* This pair of nerves consists of both motor and sensory fibers which have their origin in the hindbrain. Each trigeminal nerve has sensory and motor roots, with a large ganglion (Gasserian) on the sensory root. The two roots of each nerve unite distally to the ganglion, and then the nerve divides into three main branches with motor and sensory fibers (opthlamic, inferior maxillary, superior maxillary) that terminate in the muscles and sense cells of the eyes, tongue, jaws, and skin of the face.

VI. *Abducens.* A small pair of nerves, primarily motor in function, which innervates one pair of the eyeball muscles but, possibly, also carries afferent

sensory fibers from these same muscles. Origin in hindbrain, near the posterior margin of the pons.

VII. *Facial.* An important pair of cranial nerves carrying motor fibers which innervate various muscles of face and scalp; also sensory fibers are present carrying afferent impulses from the taste buds of the tongue. Origin in hindbrain, just posterior to the abducens (VI).

VIII. *Auditory.* The auditory nerves contain only sensory fibers that carry auditory and equilibratory impulses to the central nervous system. Each auditory nerve divides into two main branches: the *vestibular*, which innervates the semicircular canals, and the *auditory*, which innervates the cochlea. Origin in hindbrain, just posterior to the facial (VII).

IX. *Glossopharyngeal.* Both motor and sensory fibers are present in this pair of nerves. The former control muscles in the pharynx concerned with the process of swallowing and also motor elements in the salivary glands. The sensory fibers innervate the taste buds in the posterior third of the tongue, together with certain membranes lining the pharynx. Origin in hindbrain, in close association with VII and VIII.

X. *Vagus.* This is a large and important pair of nerves containing both motor and sensory fibers. The motor fibers of the vagus are important in the control of heart action and also of the muscle tissue in certain regions of the alimentary canal, notably the larynx (speech), esophagus, stomach, and small intestine. Efferent vagus fibers are also concerned with the secretions of the gastric glands. Sensory fibers of the vagus innervate the arch of the aorta and aid in maintaining proper blood pressure.

XI. *Spinal Accessory.* This pair of cranial nerves innervates certain muscles of the shoulder region. Sensory fibers also carry afferent impulses from these muscles. Origin, partly in medulla and partly from anterior portion of spinal cord.

XII. *Hypoglossal.* This final pair of spinal nerves carries motor and sensory fibers which innervate certain tongue muscles.

Cuvier. See Comparative Anatomy.

Darwin, Charles. See Organic Evolution.

Darwin, Erasmus. See Organic Evolution.

Diffusion. "Diffusion is the process by which molecules in the gaseous or liquid state tend to attain a uniform distribution throughout the region acessible to them. Diffusion of gases is familiar. Diffusion of solutes in the solvent is not so often noticed because the process is comparatively slow and is commonly hastened by stirring; but, given time enough, any solute can become uniformly distributed in its solvent without any mechanical aid to diffusion. This results in equal concentration in all parts except in so far as prevented by surface tension, adsorption, or other interfering factors. Diffusion is a necessary accompaniment to the equal partition of energy between molecules which is completely attained in any system only when each species of molecule or ion is uniformly distributed.

"In living matter and in many other colloidal systems, however, the interfering structures in the form of micellae, gels, and membranes make the non-

uniformity of distribution of molecules and ions more significant than is the tendency to equal distribution. Inequalities of distribution in living things have important consequences. Among them is the development of osmotic pressure which partly determines the movement of water in and out of cells. Furthermore, localized concentrations of fat or carbohydrate and of enzymes and other reactants in the cell are of importance in regulating vital chemical reactions. The definitely restricted concentration of ions resulting from colloidal structure causes accumulation of electrical charges so that potential differences arise and produce the electrical phenomena of life. Other consequences of the interferences with free diffusion might be mentioned, but these are sufficient to draw attention to the physiological significance of colloidal structure.

"Of the factors that prevent free diffusion in living things, membranes have attracted especial attention. The belief that matter can be alive only when enclosed in protective cell membranes has become more and more firmly established by all the developments of physiology since the statement of the cell theory (1833–1839). Fundamental qualities of living matter are dependent upon some protection from the environment. Metabolism is constantly proceeding, so that the chemical composition of living matter is ever changing. Yet these changes must be largely reversible; for the chemical composition of every bit of protoplasm varies only within the narrow limits that permit the maintenance of that integrity of composition consonant with the highly developed individuality of every different kind of living structure. Maintenance of integrity demands that protoplasm shall constantly "select" its specialized requirements and "reject" other materials, while providing simultaneously for ejecting its equally specialized products and wastes. Free diffusion between protoplasm and its environment spells instant death. The limiting membrane of protoplasm appears to be the very guardian of life, not a mere dead partition. Its intricate architecture has so far defied all attempts at artificial imitations, even though membranes possessing some of the properties of living ones can be prepared. Hoping eventually to understand the nature of living matter, one finds no problem more alluring than those relating to the nature and behavior of cell membranes. No wonder, then, that a considerable portion of physiological research in recent years has been devoted to such studies.

"One reason for belief in the existence of protoplasmic membranes is furnished by the phenomena of bio-osmotic pressure. Living cells can exhibit internal pressures such as are developed by an artificial sac composed of a semipermeable membrane containing a solution and immersed in water. Although the pressure in cells is explained by some physiologists as due to imbibition and this doubtless is one of the forces involved, yet much evidence points to osmotic pressure as an important factor and sometimes the predominating one in the production of intracellular pressures. It thus gives presumptive evidence for the existence of protoplasmic membranes. Osmotic pressure is one of the forces that determine the movements of water into and out of living structures. This, as previously explained, has important effects

on every type of vital activity so that an attempt to understand its fundamental nature is worth while.

"To begin with, one should recall the kinetic conception of matter that postulates, in accordance with the laws of thermodynamics, that all molecules are constantly in motion which could cease only at a temperature of absolute zero. As a corollary of this idea, we conceive of the molecules of matter in the fluid state as exhibiting not only vibratory motion but translatory motion as well. This results in the phenomenon of diffusion. Suppose, however, that the solution is in contact with a semipermeable membrane, permeable to the molecules of the solvent but not to those of the solute. The conditions that then prevail are typified by the following specific instance. Suppose a dialyzer is provided with a copper ferrocyanide membrane that is permeable to water but impermeable to sugar. On one side of the membrane is a 10 per cent sugar solution, and on the other is distilled water. Computing on the basis of the molecular weights of water (18) and sugar (342), we find that there are approximately 169 molecules of water in the solution to 1 of sugar. Molecular motion results in the continual bombardment of the membrane on both sides; but out of every 170 hits on the inside, 169 are made by water molecules and 1 by a sugar molecule, whereas, on the outside, all hits would be made by water molecules alone. Since the membrane is permeable to water but not to sugar, the chances are in favor of the passage of water from the outside to the inside of the membrane. The actually observed result is in accord with this conception, because the level of the solution inside the dialyzer rises. The solution then exerts a pressure measured by the difference in level between it and the water outside the membrane. This is osmotic pressure." (Mitchell, "A Textbook of General Physiology," pp. 433–437, McGraw-Hill Book Company, Inc., New York, 1938.)

Diphtheria Antitoxin. Consideration of the preparation of diphtheria antitoxin in the horse will serve as an example of methods used in the preparation of various other antitoxins. As the first step in the process, it is necessary to secure the toxin produced by the diphtheria bacilli. This is accomplished by the cultivation of pure laboratory cultures of the bacilli in the proper nutrient solution. The growth of the bacteria is accompanied by the liberation of the diphtheria toxin in the nutrient solution just as occurs in the tissues of the body. The increasing strength of the toxin can be determined from time to time by injecting a measured amount into a guinea pig of standard weight and noting the length of time it takes to kill the animal. This unit of toxicity, known as the *minimum lethal dose* (M.L.D.), is the least amount that will kill a standard guinea pig in a certain time. When the toxicity of the solution has reached the desired standard, the diphtheria organisms are killed and then filtered off from the nutrient solution in which they have grown and that now contains the diphtheria toxin.

The next step involves the transfer, over a period of some days, of measured amounts of the toxin to the horse. Only a comparatively small dose of this extremely powerful poison can be tolerated at first, but, as the tissues react by the synthesis of antitoxin, the amount of diphtheria toxin injected

into the horse can be gradually increased without danger. When the antitoxin in the horse's blood has reached the optimum strength, the horse is bled. Several quarts of the blood containing the diphtheria antitoxin can be secured without injury to the animal; then the blood corpuscles are removed; and, finally, the serum obtained after the plasma has clotted. The blood corpuscles thus removed are usually restored at once to the vascular system of the horse. The production of antitoxin, as just described, does not injure the experimental animals, so that the horses may be used for years in the production of antitoxin, as described in the following interesting quotation from the *New York Times.*

"'Old Doc Dobbin,' a large black work-horse, whose life was considered a notable contribution to public health, is dead. He died suddenly today in his stable at a biological laboratory near New Brunswick where he was employed to supply antitoxin material for the treatment of children against diphthera.

"'Old Doc,' a native of the Western Plains, was 21 years old. During his lifetime his blood had supplied antitoxin for the treatment of more than 41,000 children. Two years ago he was the guest of honor at a birthday party attended by school children of the city. At that time 'Old Doc' was escorted to a table decorated with apples and a huge cake decked with candles. Greeted with 'happy birthdays' and congratulations, Dobbin munched a big red apple while a eulogy for him was delivered.

"A 12-year-old-bay, known as 'Mickey,' has been chosen as the successor of 'Old Doc' at the farm where 150 horses are kept for making antitoxin. Mickey, too, hails from the Western Plains and was chosen because of the strength of the serum made from his blood and his strong constitution. The successor to 'Old Doc' is gentle despite his weight of nearly 1,400 pounds, and has been on the laboratory farm for five years."

Dissociation. "It has been found that acids, bases, and salts, when dissolved in water, have the power to conduct an electrical current, whereas certain other substances, for example, sugar, fail to do so. It has also been found that the substances that conduct the electrical current when in solution exert, for the same molecular concentration, a higher osmotic pressure than substances that do not conduct the electric current.

"It was suggested by Arrhenius that substances that conduct the electric current do so by virtue of the fact that in solution there is a splitting of their molecules into two or more portions, atoms, which, becoming associated with a number of molecules of water, are called *ions.* These then behave like molecules, so far as diluting the solvent is concerned. These ions are of two sorts: those bearing positive charges, the cations; and those bearing negative charges, the anions. The names of the ions receive their respective prefixes from the fact that, if electrodes are placed in a solution of an electrolyte and a current is passed through the circuit, it is found that the ions bearing the positive charges, such as H^+, Na^+, Ca^{++}, collect and even give up their charges at the cathode, and those bearing the negative charges, such as Cl^-, SO_4^{--}, CO_3^{--}, at the anode. From what has just been said, it will appear that in a

solution of an electrolyte three varieties of particles are present: positive ions, or cations; negative ions, or anions; and undissociated molecules. The degree to which the dissociation may take place is, of course, a variable and depends upon a variety of factors, such as the nature of the substance and its concentration in the solution.

"Dr. Lewis Jones has given a very vivid picture of the processes that go on in an electrolytic solution when an electric current is passing. He likens the molecules in solution to dancing couples on the floor of a ballroom. Here and there couples are separated, and the isolated individuals are moving about by themselves. Suppose a mirror at one end of the room and a buffet at the other; the ladies will gradually accumulate around the mirror and the gentlemen around the buffet. Moreover, the dancing couples will gradually be dissociated to follow this movement. Although Dr. Jones's example gives a good picture, it should not be taken too literally, for not all dissociations are of the same type. It is of importance for the student of physiology to remember that

1. All acids give a free H^+ ion.
2. All bases give a free OH^- ion.
3. All sodium salts give a free Na^+ ion.
4. All potassium salts give a free K^+ ion.
5. All calcium salts give a free Ca^{++} ion.
6. All ammonium salts give a free NH_4^+ ion.
7. All nitrates give a free NO_3^- ion.
8. All chlorides give a free Cl^- ion.
9. All sulphates give a free SO_4^{--} ion.

"The degree to which any electrolyte dissociates in solution depends very largely upon the degree to which the solution is diluted. For example, at infinite dilution such a salt as potassium chloride would be completely dissociated so that there would be twice as many particles in solution as there were molecules originally introduced. The solutions that the physiologist uses, however, are not infinitely dilute—and do not contain completely dissociated salts. The dissolved salt molecules are, in general, dissociated to about 86 per cent.

"The ionic condition is of great importance in living matter because, in the living substance, so many different substances are brought into close relations. There is great opportunity for a vast number of new ionic combinations to be formed. The formation of these new combinations is a part of the normal metabolic activity of every living organism.

"In the solutions that will be dealt with here, water is the principal solvent. It is the one universal solvent. It is not only the chief constituent of living organisms, but it is, as well, the solvent and carrier of the chief food and excretory products. In it, in the animal body, are dissolved gases; inorganic salts; a great variety of organic compounds, including carbohydrates and proteins; products of digestion, such as amino acids and simple sugars; and various metabolic wastes. Henderson well states: "Indeed, as clearer ideas

of the physical-chemical organization of protoplasm have developed, it has become evident that the organism itself is essentially an aqueous solution in which are spread out colloidal substances of vast complexity."

"Water is not only a solvent, but it is itself an electrolyte. A few of the H_2O molecules dissociate into H^+ and OH^- ions. The number of the molecules so dissociated is relatively very small and is measured by the concentration of H^+ or of OH^- ions in the water. At temperatures of 22 or 23°C., this dissociation is sufficient to give 1 g. of weight of free H^+ ions in 10,000,000 liters of water, that is, a solution having a concentration of $N/10{,}000{,}000H^+$. Inasmuch as there is an equal concentration of OH^- ions in the solution, the liquid will be neutral in reaction. And since this dissociation of molecules occurs, water may be spoken of as an electrolyte.

"Water seems to aid also in the dissociation of the molecules of many substances that may be dissolved in it. Such substances are spoken of as *electrolytes* because they will conduct an electric current.

"Other properties possessed by water that render it valuable as a component of living matter are its

1. High surface tension, exceeded only by that of mercury.
2. Low internal friction, resulting in low viscosity.
3. Great heat capacity.
4. High heat conductivity.
5. Latent heat.
6. Greatest density at 4.0°C.

(Rogers, "Textbook of Comparative Physiology," pp. 14–17, McGraw-Hill Book Company, Inc., New York, 1938.) See Matter; Hydrogen Ion.

Earthworm. "Earthworms, of which there are a great many species widely distributed in the soil of practically every region of the globe, belong to a phylum of segmented animals known as the Annelida. Due to the fact that the Earthworm possesses a number of structural features which are of considerable importance in interpreting those of still higher types of animal life, it is an especially valuable form for study. These structural features may be enumerated as follows:

"The Earthworm is a triploblastic animal; the three primary germ layers, ectoderm, mesoderm, and endoderm, being present as in higher animals, and in contrast to diploblastic animals like Hydra.

"The Earthworm possesses a body cavity, or coelom, lying between the body wall and the tubular alimentary canal. Thus, the body plan may be described as a tube within a tube. This type of structure is present in higher forms, but it is not found in the Coelenterates, in which the body may be said to consist of a single tube.

"The Earthworm shows a definite segmentation, or metamerism, of the body; that is to say, the body is composed of a large number of distinct segments which are arranged in a linear series. Varying degrees of segmentation are present in most of the higher forms of animals.

"The Earthworm shows a two-sided, or bilateral, symmetry. As a rule, the organs in such a case are paired: one situated on the right side of the body and one on the left side. Accordingly there is only one plane which will divide the animal into symmetrical halves. Bilateral symmetry is even more pronounced in the higher animal types.

"The Earthworm possesses a number of highly developed organ systems for performing various vital functions, such as nutrition, transportation, excretion, etc. These arise by a grouping of certain tissues, and are characteristic of all the higher organisms." (Baitsell, "Manual of Animal Biology," p. 81. The Macmillan Company, New York, 1932.)

Electrocardiogram. "A graphic record of the electrical variations produced by the beating heart is called an *electrocardiogram*. These variations are the result of the development of electrical negativity of excited muscle as compared with unexcited tissues. The electrical variations of the heart are thus entirely comparable to the negative variation or action current of other muscles. When the skeletal muscles are at rest, save for quiet breathing movements, the action currents of the heart can be satisfactorily recorded and accurately measured by means of a string galvanometer. Such an instrument, when especially adapted for observations on the heart, is called an *electrocardiograph*. The movements of the string of the galvanometer are photographed upon a moving sensitive film to give the electrocardiogram. The changes of electrical potential in the heart can be communicated to the galvanometer through electrodes applied to the surface of the body. This is the case because animal tissues and fluids are able to conduct electrical currents. Large nonpolarizable electrodes are applied to the two hands or to one hand and one foot in order to connect the human body to the apparatus. In studies upon experimental animals, small nonpolarizable electrodes can be applied to definite locations of the exposed or excised heart. The electrocardiograms that have been obtained by this latter method have been especially useful in studies designed to show the point at which the heart beat originates and to show the course that the wave of contraction takes as it progresses over the heart muscles. (Mitchell, "Textbook of General Physiology," pp. 589ff., McGraw-Hill Book Company, Inc., New York, 1938.)

Electrolytes. See Dissociation.

Electrons. See Matter.

Energy. "The phases of reality with which the student of science has to deal are matter and energy. The term commonly used to distinguish force is *energy*, and by energy is meant the ability or the power to do work. It will be noted that the word energy involves the concept of motion, either existent or potential. Some of the earlier writers believed not only in the existence of forms of matter that had no common factor but in different manifestations of force, which were not and could not be related to each other. The necessary conclusion now is not only that all matter is composed of the same sorts of ultimate units but also that all forms of energy have a common origin, the energy of the electron; that is, matter and energy are but different manifestations of the same thing (electricity).

"Energy is found to exist in two chief types:

1. Kinetic energy, the energy of motion.
2. Potential energy, the energy of position.

"Energy of motion appears in a variety of forms, as electrical, magnetic, atomic, molecular, radiant, chemical, gravitational, mechanical, and thermal. It is possible that all these different manifestations may be explained upon the assumption of the energy of the electrons. It is certainly not difficult to transform one form of energy into another. Some authors would add to the list given biotic energy, as a distinct form of energy found only in living matter. This, too, may be derived from the energy of the electrons that make up the living matter. At any rate, there is not at the present time sufficient reason for distinguishing this form of energy from the chemical energies of the substances that are to be found undergoing change in the living substance.

"Energy of position may be that of a weight in an elevated position, which may, if properly harnessed, accomplish work when allowed to move; or it may be that of electricity accumulated in a storage battery or the energy of chemical substances that may be released in the formation of some new chemical substances; or that of food substances that may be transformed, with the production of heat or light or electricity or the accomplishment of work; or that of storage substance in living cells, which, when drawn into the vortex of the metabolic activities of the cell, may furnish the energy for the performance of a great variety of cellular activities.

"Energy of one form may, under suitable conditions, be converted into energy of another form. Thus, kinetic energy of moving air or of falling water may be converted into electrical energy. By the use of the proper type of transformer, the electrical energy may be converted into mechanical, thermal, or radiant energy. The energy of the sunlight may, in a similar way, be converted into mechanical energy, or it may be stored up by the green plant and form a supply of chemical potential energy. The energy of chemical compounds, bound in the molecules through the attractions of the different atoms for one another, may be transformed into heat energy or mechanical energy. In all these transformations of energy, there appears to be a tendency for energy to be degraded into heat. All forms of energy may ultimately appear as heat, but it does not seem possible at present to convert heat energy into all the other forms of energy.

"Any physical system through which energy is transformed from one sort to another may be spoken of as a *transformer*. Such transformers are of great variety—some very simple, and some very complex. Many machines have been constructed as the result of human ingenuity. These serve in a mechanical way as energy transformers. Many energy transformers are the result of long-continued evolutionary processes, dealing in particular with what is commonly known as *living matter*. It has been customary to think of living cells as the most wonderful of these energy transformers and to attribute to them very special powers and properties because of the things they have been observed to do. Living cells are themselves highly complex colloidal systems.

As such, they exhibit properties that are common to other colloidal systems. Among these properties is the ability to synthesize more complex substances out of their less complex components. The more there is discovered concerning the nature of the living substance the more likely it seems that the inorganic colloids are the substances that must be looked to for the first appearance of those remarkable energy transformations commonly attributed to living cells. The very intimate way in which the components of the colloidal systems are related to one another and the great expanse of internal surface exposed render the colloidal condition ideal for transformations of both material and energy. Certain it is that some of the inorganic colloids, such as ferric hydrate, have the power to synthesize carbon dioxide and water into more complex molecules. It has been shown that the synthetic power of the chloroplast of the green plant is due, not to the chlorophyll held in the chloroplast, but to an iron compound of a simpler sort. The earliest forms of matter that had the power to synthesize even very complex substances must have been very simple as compared with the simplest forms of living matter as known at the present time. The fact is also becoming apparent that, in living cells, chemical operations are initiated and controlled not by the active protoplasm as a whole but by certain special substances produced by the activity of the protoplasm, termed *enzymes*. These are the energy transformers of living matter." (Rogers, "Textbook of Comparative Physiology," pp. 10–12. McGraw-Hill Book Company, Inc., New York, 1938.)

Enzymes. The inauguration of the modern science of enzymology began to take shape during the first half of the nineteenth century. Scientific methods of study were applied to a variety of phenomena that common people had accepted for centuries: the use of yeast to leaven bread or ferment wine; the digestive action of the stomach juice; the ability of organs supplied only from the blood to produce a multitude of different chemical substances, as in saliva, milk, or urine. Simultaneously, in the field of inorganic chemistry, came the recognition that certain chemical reactions were peculiar in that their progress was profoundly affected by the presence of some ingredient that apparently remained itself unchanged. A little sulphuric acid facilitated the breakdown of starch into glucose; hydrogen peroxide decomposed with great rapidity in the presence of an apparently inert substance like platinum.

In 1837, Berzelius recognized that the many diverse phenomena outlined above had in common a single feature which he described as an unknown chemical "force": the ability of a substance present in relatively small amounts to cause an enormous increase in the rate of a chemical reaction. Berzelius proposed the term *catalysis* to describe such reactions which take place, therefore, under the influence of a catalyst. The term catalyst was thus from its inception applicable to similar phenomena in the organic and inorganic worlds alike. Indeed, Berzelius predicted the fundamental part that must be played by catalytic processes in living plants and animals, a prediction that has since received overwhelming verification.

At this time, the organic catalyst that received the greatest attention was what was then known as the *yeast ferment*, responsible for alcoholic

fermentation. Berzelius still believed that yeast was a nonliving substance; but in the same year, Cagnaird-Latour, Theodor Schwann, and Kützing discovered, independently of each other, that yeast was a microscopic form of life. For some time after this, the word *ferment* was reserved for such cases in which the presence of uninjured cells was supposed to be essential for the action of the organic catalyst. Active extracts, such as malt, or secretions, as of the stomach, were frequently referred to as *unorganized* or *unformed* ferments. In order to clarify current concepts, Kuhne, in 1878, proposed that the word *enzyme* should be used for the unorganized ferments. All confusion was finally resolved in 1897, when Büchner was able to show that extracted juices of yeast contained the yeast ferment; the term *ferment* and *enzyme* thus came to mean the same thing and are used interchangeably at the present day, although, in English-speaking countries, the latter is more generally accepted.

In accordance with Berzelius, it is customary to introduce the student to the concept of an enzyme by pointing out that it is an organic catalyst. Some authors prefer to elaborate this statement by saying that an enzyme is an organic catalyst present in or produced by living organisms. Furthermore, the statement that enzymes are produced by living cells must, at best, be only a partial truth; the growing acceptance of the idea that enzymes are as essential in the building up as in the breakdown of protoplasm would suggest the existence of some more intimate relationship. Indeed, some authors, as, for example, Wright, have speculated on the possibility of a close connection between the genes, or genic complexes, which determine the hereditary potentialities of the organism, and the intracellular constructive enzymes which effect the practical realization of these potentialities.

The essential feature, common to all catalyzed reactions, is, as already explained, the effect of the catalyst on the rate of the reaction. In all the more familiar cases, this effect is one of pronounced acceleration, but it is important to bear in mind that the effect may equally well be one of retardation; the term *negative catalysis* being applied in such cases. According to the generally accepted theory, no catalyst can initiate a reaction, nor can it change in any way the state of equilibrium that marks the completion of the reaction. On this basis, therefore, the sole action of a catalyst is upon the rate at which chemical equilibrium is attained. In practice, however, in the absence of a positive catalyst, a reaction rate may be infinitely slow and the effect of the catalyst thus frequently appears to be an initiation as well as an acceleration of the reaction. It is this feature of enzyme actions which makes them such important factors in the metabolism of living organisms; reactions that can be performed in the laboratory only with great difficulty, if at all, and then frequently only with the aid of high temperatures and powerful reagents destructive to life, can be performed with the greatest ease and efficiency by living cells.

The concept of a catalyst as an agent that changes the rate of a chemical reaction is accompanied by the postulate that catalyzed reactions must obey the laws that govern chemical processes. The fact that these laws are not

always followed by enzymic reactions has, in the past, greatly impeded the progress of knowledge in this field. One difficulty in the way of critical investigation of the kinetics of enzyme action has been the relative impurity of the enzyme preparations. A major achievement of the last decade has been the development of suitable technical methods for the concentration and isolation of enzymes.

A crystalline preparation of the enzyme urease was isolated by Sumner in 1926. Urease is responsible for the breakdown of urea with the liberation of ammonia and carbon dioxide. It is abundant in certain seeds, like soybean and jack bean from which it is conveniently isolated. A bacterium, *Micrococcus ureae*, utilizes this enzyme to split the urea that is excreted as nitrogenous waste in the urine and is thus responsible for the ammoniacal smell of stale urine.

Crystalline urease proved, upon examination, to be a protein of the globulin group. Formerly there had been much dispute as to whether or not enzymes were of a protein nature, and, since much supposed evidence had been accumulated to the contrary, Sumner's discovery did not immediately receive a ready acceptance. It was not long, however, before parallel results were obtained through the isolation of other enzymes in pure, or relatively pure, crystalline form; the most important contributions, perhaps, being those of Northrop and his coworkers, beginning in 1930 with the isolation of crystalline pepsin. Although great progress has been made, it must be admitted that the study of purified enzymes is still in its infancy; the fact that the best known preparations have all proved, up to the present time, to be proteins or simple protein derivatives must not be taken to exclude the possibility that other types of organic compound may also function as enzymes. Furthermore, the dispute remains as to whether the protein is itself the enzyme or merely an essential carrier for an active (prosthetic) group. In Northrop's laboratory, it has been shown that any reaction that destroys or radically changes the protein causes, in similar proportion, a corresponding loss of enzyme activity. Such experiments strongly support the view that the protein is itself the enzyme. In order to function as a catalyst, it is evident, however, that the protein must possess some quite special configuration of the molecule, the key, as it were, to the catalyzed reaction. Active groups attached to a protein molecule have been demonstrated in the case of certain respiratory enzymes, and the distinction between a prosthetic group that is loosely attached and one that forms a more integral part of the protein molecule may, after all, be an academic rather than a fundamental concept.

It is important for the student of living matter to have a clear idea of the nature of reversible chemical reactions. It is misleading to think of a chemical reaction as a process that continues to completion in one direction; however near to completion the end point may be, it is nevertheless an equilibrium. Reactions can only proceed to completion when the products are continually being removed from the scene of the action. Large numbers of reactions, especially in the field of organic chemistry, do not proceed to an end point that

even remotely resembles completion. Such reactions are known as *balanced*, or *reversible, reactions;* a state of equilibrium is reached, for example, when the rate of combination of two substances A and B to form the compound AB is exactly balanced by the tendency of AB to decompose with the formation of A and B. It will be evident from general considerations, without the application of mathematical formulae, that the relative amounts of A, B, and AB that may be present in the mixture at equilibrium must depend in part on the relative rates of the two opposing reactions, in part on the initial concentration of the ingredients at the start of the reaction. An irreversible reaction can, from this point of view, be regarded as one in which the rate of the opposing reaction is negligibly small. It will be clear, in the case of all reversible reactions, that equilibrium may be reached from either direction; by breakdown, if the product AB is in excess at the start; by combination, if the breakdown products A and B are in excess.

Whenever a catalyzed reaction is of the reversible type, the action of the catalyst is to accelerate (or, in rare cases, retard) the rate at which equilibrium is attained. A catalyst must therefore facilitate both the combination and the breakdown phases of the reaction in equal measure, since it has no effect whatever on the final state of equilibrium. If enzymes are true catalysts, it is evident that this important concept should be applicable to large numbers of reactions taking place within the living organism. Furthermore, an enzyme should be able to effect either breakdown or synthesis according to the conditions under which it is permitted to operate. In a few well-established cases, the reversible nature of enzymic catalysis has been clearly demonstrated. Enzymes known as *phosphatases* facilitate the reactions that take place between phosphoric acid and certain organic substances such as sugar or glycerin. An extract containing intestinal phosphatase can, in the presence of sodium phosphate and glycerin, effect a partial synthesis of sodium glycerophosphate. Conversely, in the presence of sodium glycerophosphate, it will effect a partial breakdown to glycerin and sodium phosphate The equilibrium will be the same in either case, in accordance with the laws governing such reactions. If one of the end products is continuously being removed, the reaction could be carried to completion in either direction. This is presumably what actually happens at the surface of the intestinal mucosa; the breakdown products are absorbed by the intestinal epithelium and transferred to the blood or underlying tissues; and this process continues until digestion of those organic phosphates which form the substrate for this reaction is completed.

The reversibility of enzyme action has been demonstrated in relatively few cases; its theoretical importance is, however, outstanding. Various examples will occur to the student as being readily susceptible to interpretation along these lines. Thus, during the day, the green leaf of a plant stores up starch because glucose is being formed by photosynthesis more rapidly than it can be distributed and utilized. At night, the starch disappears from the leaf because the rate of removal is now in excess. It is possible, and in fact probable, that this reversible behavior is under the control of a single

enzyme complex. Similar processes may govern the storage and subsequent utilization of other temporary food reserves, for example, the temporary increase of glycogen (animal starch) in the liver after a meal when the blood is laden with sugar. The reaction in this case is the familiar union of a large number of glucose molecules to form a complex polysaccharide with the elimination of water, according to the following expression:

$$nC_6H_{12}O_6 \rightleftharpoons (C_6H_{10}O_5)n + nH_2O$$

In the case of starch the number n may be between 26 and 30; it is probably somewhat less for glycogen but is not definitely known. Synthetic proteins, the plasteins, have been prepared by Wastenys and Borsook by the reversible action of pepsin or trypsin. From the point of view of the biologist, the most significant aspect of enzymic synthesis is, perhaps, the synthesis of the complex system of protoplasm itself. Almost nothing is yet known in this field.

Protein-splitting enzymes can readily be extracted from all living cells. The conditions under which they perform this operation have been extensively studied; they differ markedly from the protein splitting enzymes of the digestive juices as noted below; for example, they are activated by substances bearing the reducing group $-SH$ (hydrosulphide) in the molecule and by hydrogen cyanide. One of the best known of these intracellular proteinases is papain, which may be extracted from the fruit of the papaya and which has recently been isolated in the form of crystals with, as might be expected, the properties of a protein. Dried preparations are sold for medicinal purposes, and the fruit has often been advertised as an aid to digestion although it is not known to what extent it can profitably be used to supplement defective secretion of normal digestive juices.

Extracellular Enzymes. Because the digestive enzymes are so powerful and so relatively easy to study, the science of enzymology has proceeded more rapidly in this field than in any other, not excepting the immense field of the respiratory enzymes. It must not be supposed that extracellular digestive secretions should figure as largely as they do in a balanced survey of organic catalysis. The ability to form and secrete extracellular enzymes appears rather to be a special property which has been evolved in various ways by different types of living organisms. Extracellular enzymes are not produced at all as a rule by green plants. It is possible that a few plants that live in nitrogen-deficient environments and that supplement their normal holophytic methods of nutrition by the assimilation of the decomposition products of captured organisms may also produce extracellular digestive secretions. This is denied in the case of the pitcher plant; the activities of other carnivorous plants, the sundew, flytrap, and bladderwort, certainly call for reinvestiga tion in the light of modern methods of microenzymology.

The colorless plants, such as fungi, molds, yeasts, and bacteria, typically liberate powerful extracellular enzymes which effect the breakdown of organic substances in their environment. The products of hydrolysis can then be taken up by the living cells. Many of these organisms, especially among the

yeasts and bacteria, are either facultative or obligatory anaerobes; that is, they can or must obtain their metabolic energy by some other method than the utilization of atmospheric oxygen. Many of them thus contain or secrete enzymes which can perform remarkable metabolic feats. A familiar and economically important example is the anaerobic utilization of sugar by yeast. A complex system of enzymes, activators, and co-enzymes, which, in the light of modern knowledge, must now be called the *zymase complex*, effects the breakdown of sugar into alcohol with the liberation of carbon dioxide. The reaction undoubtedly proceeds in several stages, and only its final products are expressed by the following formulation:

$$C_6H_{12}O_6 \rightarrow 2C_2H_5OH + 2CO_2$$

A surprisingly similar series of operations are apparently performed by the enzyme complexes of muscle tissue. Glucose is broken down, through a long chain of intermediary reactions, into the end product, lactic acid. The initial and final phases of the reaction can be expressed as follows:

$$C_6H_{12}O_6 \rightleftharpoons 2C_3H_6O_3$$

The similarities between the action of yeast zymase to that of muscle enzymes does not appear clearly when the end products of the two reactions are indicated crudely, as in the foregoing equations. The mode of formation of alcohol in the one case and of lactic acid in the other is nevertheless achieved through an almost parallel series of hydrolyses and transformations. In both cases, an essential intermediary step is the formation of hexosephosphoric acid; in both cases, the presence of magnesium appears to play an essential but little-understood role; in both cases a co-enzyme has been isolated, and, although not identical, they have proved to be similar kinds of substance. Finally, in both cases, a stage of the reaction can be blocked by the addition of monoiodo-acetic acid.

Special attention has been given to yeast fermentation because of its economic importance as well as because of the resemblances that it shows to processes that accompany muscular contraction. Many other microorganisms are able to produce substances of use and interest to man. Vinegar is produced from alcohol by the oxidative action of the acetic acid-forming bacterium. Another bacterium is used commercially in the fermentation of starch to form butyl alcohol. A mold, *Aspergillus niger*, assists in the production of citric and oxalic acids from sugar.

The Protozoa do not appear to secrete extracellular enzymes. Holozoic species produce digestive enzymes in their food vacuoles, whereas the saprozoic forms must live in an environment rich in the diffusible products of digestion. As we pass to the multicellular animals, there seems to have been a gradual evolution of extracellular digestion. Sponges produce no extracellular enzymes; the cells lining the gut are provided with flagellae and are able to pick up and ingest food particles in the same way as individual protozoans. Among the Coelenterates, we find the first appearance of an extracellular

digestive secretion. In hydra and among the corals, the only enzyme contained in this secretion is a protease; all other phases of digestion are carried on within the cells lining the alimentary tract that phagocytose the food particles and initial products of protein hydrolysis. The number of extracellular enzymes and the degree to which digestion proceeds in the lumen of the alimentary canal vary greatly among different groups of invertebrates. In the vertebrates, there is also evidence that some of the final phases of intestinal digestion may even be carried on within the cells of the intestinal wall.

Some animals produce remarkable enzymes that enable them to digest substances that are entirely useless as food for man. Thus snails possess an enzyme that attacks cellulose, hydrolyzing it to simple sugars. An extract of the digestive gland of such an animal cannot be filtered through ordinary filter paper because the paper itself will be digested. Wood-boring insects also can digest cellulose, and, in the case of the termites, this has been shown to depend on the presence of a symbiotic protozoan fauna and bacterial flora that inhabit the gut. The wax moth can digest beeswax, a substance that is totally resistant to the powerful lipase of the mammalian pancreas. The clothes moth has a peculiar type of proteinase which, in a strongly alkaline medium, is able to effect the breakdown of hair and horn. This enzyme is called *keratinase* because of its ability to attack these materials. Some snails and a few other invertebrates can digest the resistant material chitin, a nitrogenous derivative of carbohydrates which is an important constituent of the external skeleton of arthropods.

Proteases. The protein splitting enzymes of the digestive juices deserve special consideration. The enzyme *pepsin* was isolated in crystalline form by Northrop and has been extensively examined by this investigator and his colleagues. It is secreted from peptic cells in the gastric mucosa in an inactive form, pepsinogen, which has been isolated in crystalline form also. Pepsinogen is transformed into active pepsin by the action of hydrochloric acid secreted by the oxyntic cells of the gastric mucosa. The correlation of the type of cell, peptic or oxyntic, with the type of secretion, pepsinogen or hydrochloric acid, respectively, was achieved by the application of the modern methods of histochemical technique developed by Linderstrøm-Lang and his colleagues during the last decade. Pepsin can only attack proteins in an acid medium. Northrop believes that this is due to the fact that pepsin can react only with the positive protein ion which appears, of course, in a medium that is on the acid side of the isoelectric point. Trypsin, on the other hand, attacks proteins in an alkaline medium and would appear to react with the negative protein ion. The situation can be expressed with the aid of a simple diagram:

Thus

Partially ionized Sodium Proteinate	NaOH ⟵	Neutral protein at isoelectric point	HCl ⟶	Partially ionized Protein Hydrochloride

Or

$$\begin{array}{ccccc} - \quad + & & - \quad + & & + \quad - \\ \text{P and Na} & \leftarrow & \text{P} & \rightarrow & \text{P and Cl} \\ | & & | & & | \\ \text{(attacked} & & \text{(attacked} & & \text{(attacked} \\ \text{by} & & \text{by} & & \text{by} \\ \text{trypsin)} & & \text{papain)} & & \text{pepsin)} \end{array}$$

Although crystalline pepsin is now believed to be a pure substance, slight elements of doubt still remain. Northrop himself was able to effect a partial separation of another proteolytic enzyme which was specially active in the digestion of gelatin; this gelatinase was present in minute amounts; it was separated but never completely purified; and mystery still surrounds the true meaning of its presence and discovery.

Another and completely distinct gastric proteinase can be isolated from the stomachs of calves. This is the enzyme *rennin.* It was formerly believed that rennin was the only enzyme that could cause the clotting of milk; and as a result of this, much confusion arose in the early literature on the subject. Investigators would test the power of different extracts on the clotting of milk and would then state that the enzyme rennin was present, sometimes in the most unexpected places. For example, rennin has been listed among the digestive enzymes of many invertebrates, including spiders and earthworms. The situation was greatly clarified when it was recognised that all proteolytic enzymes can, under certain circumstances, cause the clotting of milk, some, it is true, with greater facility than others. This discovery raised doubt as to whether or not a separate milk-clotting enzyme existed in the gastric juice of young animals. Through the investigations of Tauber and others, it is now clear that a separate milk-clotting enzyme does exist, distinct from pepsin, in the fourth stomach of the calf. On the other hand, it has not proved possible to separate rennin from pepsin as a distinct enzyme in the gastric juice of various other mammals, young or old. Rennin is not present in children or in adult human beings; nor is it found in dogs or in pigs. In all these animals, the digestion of milk is apparently a function of the enzyme pepsin.

The chemistry of milk clotting is of some interest because of its practical application. Junkets are prepared by the addition of powdered preparations of calves' stomachs to warm milk. In a few hours, the junket "sets" to a semisolid mass; an insoluble substance, the curd, holds in its interstices the fluid whey. Clotting can take place only in the presence of calcium salts, which are, of course, normal constituents of milk. A simplified explanation of the course of events is as follows: The proteolytic enzyme, normally pepsin or rennin, first hydrolyzes the milk protein casein to another soluble derivative known as *paracasein;* this is apparently achieved by the splitting off of a protecting substance also of a protein nature. The soluble paracasein then reacts with calcium to form the insoluble curd *calcium paracaseinate.* Rennin has little ability to effect other proteolytic hydrolyses and is unable to carry

the process beyond the simple stage of clotting. Pepsin and other proteolytic enzymes can continue the breakdown to lower stages provided they are allowed to work at the pH suitable to their mode of action. Clotting of milk by pepsin is not observed unless the reaction is allowed to proceed in a nearly neutral medium; the reason for this is that calcium paracaseinate is redissolved by acid; and although the casein is split, no curd makes its appearance.

When the protein digest leaves the stomach, it is acted on by at least three proteases that are secreted by the pancreas; these three have all been isolated by Northrop and his colleagues in crystalline form. The pancreatic protease complex was formerly called *trypsin;* it was known to work in an alkaline medium, resulting from the secretion of sodium carbonate in the pancreatic juice, and it was believed to be more powerful than pepsin and to be able to carry the breakdown of proteins all the way to simple peptides and amino acids. Two components of the trypsin complex, trypsin proper and *chymotrypsin,* act upon native proteins and hydrolyze them, in general, to peptones and polypeptides. In this respect, they resemble pepsin, although, as indicated above, they apparently attack the negative rather than the positive protein ion. Trypsin and chymotrypsin differ markedly in their crystalline form and in other physical and chemical properties; the fact that their action on the protein digest seems, at first sight, similar is due to our lack of knowledge of the structure of the complex protein molecules and of the types of linkage that are attacked. It can be shown that the two enzymes attack different parts of the protein molecule by submitting a substrate first to the action of one of these enzymes and then to the other. If the reaction is allowed to come to equilibrium and if the two enzymes catalyzed the same breakdown, it is evident that no change would be brought about by the second enzyme. In practice, it is found that the second enzyme will continue the hydrolysis to a new equilibrium, thus showing that entirely different linkages are attacked.

In a similar way, it can be demonstrated that pepsin attacks the protein molecule in yet another way, dissimilar to the action of either trypsin or chymotrypsin. It is thus clear that all the proteolytic enzymes may be necessary for complete digestion since their actions are supplementary.

The third proteolytic enzyme of the pancreatic juice is a *carboxypolypeptidase;* this is an enzyme that splits a few dipeptides and a large number of polypeptides, all of them compounds that possess an unsubstituted —COOH group at one end of the molecule (page 537). Substitution of the $—NH_2$ group of the peptide does not prevent the action of the carboxypolypeptidase. The pancreatic carboxypolypeptidase has been isolated in crystalline form by Anson; it liberates free amino acids from that end of the peptide molecule which it is able to attack.

By the time the protein digest leaves the duodenum, it has been reduced by the pancreatic proteases to dipeptides, polypeptides, and a percentage of free amino acids. The final stages of protein hydrolysis are carried out by the intestinal juices, most active at the surface of the intestinal mucosa. The active proteolytic enzyme of the intestine was formerly believed to be a single substance, *erepsin.* As in the case of trypsin, it has now been shown to be a

complex of several distinct enzymes. None of these have been isolated in crystalline form, and the methods of separation have been of a different nature from those employed in the isolation of gastric and pancreatic proteases.

At least three different proteolytic enzymes can be recognised as distinct entities in the erepsin complex. The first of these attacks remaining polypeptides at the end of the molecule opposite to that which was attacked by carboxypolypeptidase; that is, it releases an amino acid that bears a free —NH_2 group. Enzymes of this type are known as *aminopolypeptidases.* The final breakdown of the proteins is completed by intestinal *dipeptidases* that attack the simple dipeptides, like glycylglycine, as described in the following paragraph. A third component of the erepsin complex is a little known enzyme called *prolinase,* whose peptide linkage is atypical on account of the presence of the heterocyclic amino acid proline.

Dipeptidases are enzymes that facilitate the hydrolysis of dipeptides into their component amino acids, for example, in the splitting of such substances as glycylglycine by the intestinal mucosa, according to the following scheme:

$$2\text{ glycine molecules} \rightleftharpoons \text{glycylglycine} + \text{water}$$

The student is well aware that the amino acids are the bricks out of which protein molecules are built. Although differing widely from one another in chemical composition, they have in common a particular configuration of atomic groupings at one end of their molecule; this is represented diagrammatically in the following way:

$$\left.\begin{array}{r}\text{Radicle of}\\ \text{variable}\\ \text{character}\end{array}\right\}(\mathrm{R})\text{—}\begin{array}{c}\mathrm{H}\\ |\\ \mathrm{C}\\ |\\ \mathrm{NH_2}\end{array}\text{—COOH}$$

Of these groupings, the —COOH (carboxyl group) is acidic in character, while the NH_2 (amino group) has basic properties. Amino acids can therefore behave either as acids or as bases, according to the conditions under which they are reacting (page 568). Most important of all, they combine with each other, head to tail as it were, and it is in this way that dipeptides, polypeptides, and finally, in all probability, proteins are built up. This head-to-tail linkage, which is effected with the elimination of a molecule of water, is known as the *peptide linkage.* It might be supposed that it could be attacked by the same enzyme irrespective of whether it was present in the simple union of two amino acid molecules to form a dipeptide or in the union of long chains forming polypeptides. This, however, is not the case. It seems that the configurations of parts of the molecule adjacent to the linkage are of fundamental importance. The enzyme, dipeptidase, is merely the last in a long series of enzymes, as noted above, that are involved in the breakdown of the proteins of the food to their constituent amino acids. The initial step is taken by pepsin in the stomach juice. Pepsin can carry the hydrolysis of proteins only

as far as intermediary products proteases and peptones, still of large molecular size.

Other Digestive Enzymes. It is not possible to supplement this survey of the digestive proteases with an equally extensive account of those other digestive enzymes which are responsible for the hydrolysis of carbohydrates, fats, compounds of nucleic acid, organic phosphates, and the like. A few points of interest may be mentioned. The chief starch-splitting enzyme is the pancreatic amylase; the enzyme ptyalin, found in the saliva of a few animals, including man, is believed to be identical. Amylase has recently been obtained in crystalline form and is, as might be expected from what has gone before, a protein.

The final breakdown of the disaccharide maltose, released by amylytic hydrolysis of starch and glycogen, is effected through the aid of an intestinal enzyme, maltase. The splitting of maltose releases two molecules of glucose. In a similar manner, cane sugar is split by intestinal sucrase, yielding one molecule of glucose and one of fructose. Milk sugar, lactose, is split by yet another enzyme, lactase, yielding glucose and galactose. There is evidence that, in the case of these and other intestinal enzymes, the catalysis takes place either on the surface of the intestinal mucosa or possibly within the cells themselves. The intestinal juice has very little digestive action. A weak maltase is also present in human saliva.

The action of pancreatic lipase is essential for the digestion of fats. Bile salts have an important effect on the action of lipase; they perform a double function. On the one hand, they lower the surface tension and thus facilitate the emulsion of the fat; this reduces the fat droplets to submicroscopic size and enormously increases the area of surface exposed for lipolytic action. In another capacity, the bile salts combine readily with the fatty acids that are liberated by the hydrolysis of the fat; the combination products, known as *choleic acids,* are soluble in water and readily diffusible, and it is probably in this form that the fatty acids are absorbed by the intestinal mucosa.

A weak lipase is also secreted by the stomach. It appears to be most active in weakly acid media and is destroyed by the higher acidity of the gastric juice during periods of digestion. Its function may be to attack fats left clinging to the mucosa between periods of proteolytic digestion. Pancreatic lipase is carried down into the intestine, but the intestinal mucosa does not appear to secrete a lipolytic enzyme.

The intestinal enzyme *phosphatase* supplements the action of two other intestinal enzymes. A *polynucleotidase* attacks nucleic acid, releasing substances that are, in turn, hydrolyzed by phosphatase, with the release of phosphoric acid and further breakdown products known as *nucleosides.* The latter may, in part, be further attacked by another enzyme, *nucleosidase.*

Intracellular Enzymes. A complete account of the intracellular enzymes would of necessity involve a full understanding of all the metabolic processes that occur within the living body. Such a feat could not be attempted in the scope of the present article, even if it could be claimed that knowledge was complete, which is, of course, very far from the case. After the soluble prod-

ucts of digestion have been absorbed through the walls of the intestine, they are distributed through the blood and lymph to the tissues and there utilized in various ways.

As is well known, only comparatively few of the amino acids derived from the food are required by the human body. Some 10 amino acids cannot be synthesized by the body cells and must be derived ready made from the food; the requirements for these are relatively small except during periods of rapid growth or tissue repair. Similarly, the requirements of amino acids as sources of nitrogen, sulphur, etc., are relatively small. The bulk of the amino acids undergo an enzymatic breakdown (deaminization) by which the nitrogen group $—NH_2$ is removed from the molecule and converted at first into ammonia; later the ammonia is synthesized into urea and excreted through the kidneys (page 100). The enzymes that effect deaminization are known as *amidases;* a wide variety of such enzymes can be extracted from liver and other tissues, and they are classified according to the substrate that they attack. Some attack different sorts of amino acids; others separate the $—NH_2$ group from related types of organic bases. The enzyme urease, referred to previously, is an example of a particular kind of amidase that splits the $—NH_2$ group from urea.

The intracellular *phosphatases* and *esterases* are also very interesting. Phosphatases undoubtedly play an important part in the calcification and decalcification of bone. Blood phosphatases rise to abnormally high levels in cases of rickets, when a deficiency of vitamin D is, in some little-understood way, the cause of imperfect ossification. The acetylcholine esterase is concerned in the destruction of the chemical transmitter acetylcholine that is released at nerve endings in skeletal and cardiac muscle and at the synapse (page 495). It is evident that accumulation of so potent a drug as acetylcholine would be harmful; moreover, its rapid removal is obviously essential to the recovery phase of transmission.

The vast subject of the respiratory enzymes is in reality a field to itself. Nearly all of the enzymes discussed previously have catalyzed reactions that are hydrolyses, that is, are effected by the addition (or removal) of water. The respiratory enzymes are oxidation-reduction systems which effect the transfer of oxygen (or, anaerobically, its equivalent in removable electrons from some other source) to the tissues where, in the last analysis and under the influence of yet other oxidizing enzymes, it is finally used to complete the breakdown of carbohydrates and fats, with equivalent release of energy. The enzymes involved in these respiratory processes must be subjected to arbitrary classification. In the first place, there are the *oxidases* whose function is to activate molecular oxygen. They function only in the presence of a substance that can receive the activated oxygen. Oxidases appear to owe their ability to activate oxygen to the presence of an iron-porphyrin, or prosthetic hematin, group.

Although the hemoglobin of the blood is not usually treated as an enzyme, it shares many features in common with the oxidases. Hemoglobin is a protein to which is attached a prosthetic iron-containing hematin group. By

virtue of this group, the hemoglobin (like the oxidases, perhaps), is able to enter into labile union with molecular oxygen. In the presence of oxygen acceptors in the tissues, hemoglobin gives up its oxygen and reappears in the reduced form. Like the oxidases, hemoglobin is inactivated by cyanide which reacts with the prosthetic group. The differences between hemoglobin and an oxidase reside chiefly in the fact that the intermediate stage, corresponding to the hypothetical "enzyme-substrate" combination, is prolonged and is, in fact, carried from the lungs to the tissues by the blood stream. In the case of oxidases, the intermediary compound, if formed, is ephemeral. It is by no means certain that hemoglobins cannot in some cases behave as oxidases; thus, red muscles contain a hemoglobin that may act as a temporary oxygen reserve but may equally well play an essential role in the transfer of oxygen to the tissue.

Interesting examples of oxidizing enzymes are those which are responsible for the formation of brown or black melanin pigments through the oxidation of tyrosine. Such enzymes are referred to as *tyrosinases;* it is tyrosinase that causes the blackening of potatoes and other vegetables when they are cut and left exposed to the air. An animal tyrosinase ("dopa-oxidase") is responsible for the development of melanin in the skin (page 400). Onslow was able to show that albino rabbits, which are genetically recessives, lack the enzyme, while dominant albinos possess enzyme plus an enzyme inhibitor.

Tissues also contain enzymes that effect oxidations not by the addition of oxygen but by the removal of hydrogen from the substrate. Such enzymes are known as *dehydrogenases.* They can act only in the presence of a substance capable of accepting hydrogen. Oxygen can act as a hydrogen acceptor, but, in the absence of oxygen, other reversible hydrogen acceptors occur in tissues. In the laboratory, methylene blue has frequently been used as a labile hydrogen acceptor; it is readily reduced to a colorless compound. A number of important dehydrogenases have been studied in various tissue preparations; one of the first discovered was the Schardinger enzyme of milk. The so-called "yellow enzyme" extracted from many types of tissue appears either to be an oxidase or to behave like methylene blue as a hydrogen acceptor in relation to other tissue oxidases. It does not contain iron but is a protein which has a labile prosthetic group, the yellow vitamin B pigment, riboflavin, in combination with phosphoric acid (page 59).

$$\begin{array}{c}\text{Reduced} \\ \text{substrate}\end{array} + \begin{array}{c}\text{Hydrogen} \\ \text{acceptor}\end{array} \rightarrow \begin{array}{c}\text{Oxidized} \\ \text{substrate}\end{array} + \begin{array}{c}\text{Reduced} \\ \text{acceptor}\end{array}$$

Or

$$XH_2 + Y \rightarrow X + YH_2$$

The foregoing scheme represents the reaction catalyzed by a dehydrogenase in the presence of a hydrogen acceptor. If the hydrogen acceptor is molecular oxygen, it will be seen that the reaction takes place as follows:

$$XH_2 + O_2 \rightarrow X + H_2O_2$$

There is no doubt that such reactions must occur under aerobic conditions in living tissues, and, since hydrogen peroxide is a toxic substance, the importance of enzymes capable of effecting its removal is evident. The enzyme catalase is present in almost all tissues and liberates molecular oxygen and harmless water by decomposition of the hydrogen peroxide.

Considerations outlined above lead to the conclusion that oxidizing and reducing enzymes provide complementary mechanisms that, together, regulate the respiratory processes of the cell. Respiratory pigments, known as *cytochromes*, are found in the cells of all except anaerobic organisms. Keilin has developed the theory that the cytochromes form an essential link between the oxidases and the dehydrogenases since, like hemoglobin, they can take up and release oxygen according to the needs of their immediate environment. Compounds bearing the —SH group also appear to have an important intermediary part in the respiratory mechanism of the cell. The best known of these substances is glutathione, a tripeptide which has been synthesized.

The ultimate result of tissue oxidation is always the release of energy. As a rule, this energy is either utilized in cell metabolism or released in part as heat. The enzyme *luciferase*, which is found in many luminescent organisms, effects the removal of hydrogen from a substrate of unknown chemical composition that is called *luciferin;* the oxidation takes place according to the following scheme with oxygen behaving as a hydrogen acceptor; it is accompanied by the production of light:

$$\text{Luciferin} + 0 \rightleftharpoons \text{oxyluciferin} + H_2O$$

The most familiar example of the production of light by an organism is of course the case of the firefly. Many other luminous plants and animals are known.

Another enzyme connected with respiration is found in the red blood cells from which it may be extracted in a partially purified form. This enzyme, *carbonic anhydrase*, facilitates the release of carbon dioxide from carbonic acid according to the following equation:

$$H_2CO_3 \rightleftharpoons CO_2 + H_2O$$

Carbon dioxide is thus readily released; as fast as it can be removed in the air exhaled from the lungs. (Pickford, Osborn Zoological Laboratory, Yale University, New Haven, Conn., January, 1940.)

Evolution. See Organic Evolution.

Galen. See Biology and Medicine.

Germ Plasm. "Although clearly suggested by a number of workers, the conception of the continuity of the germ cells—or germ plasm—was first forced upon the attention of biologists and given greater precision by Weismann (1834–1914) in a series of essays culminating in 1892 in his volume entitled *The Germ Plasm.* He identified the chromatin material which constitutes the chromosomes of the cell nucleus as the specific bearer of hereditary characters, and emphasized a sharp distinction between the cellular derivatives of the fertilized egg—on the one hand, the somatic cells

which by division and differentiations build up the body of a higher plant or animal; and on the other, the germ cells which are destined to play but little part in the life of the individual which bears them, but instead are to be liberated and give rise to the next generation. The importance of this distinction can hardly be overemphasized, for at once it makes clear that, for all practical purposes, the bodily characteristics of an individual are negligible from the standpoint of heredity, since the offspring are descendants not from the body cells, but from the germ cells and these in turn from the germ cells of the preceding generation. As Weismann insisted, this view makes it difficult to conceive how modifications of the soma can so specifically affect the germ cells which it bears that the latter can reproduce the modifications—in other words that so-called 'acquired characters' cannot be inherited. And there is no satisfactory evidence that such characters are inherited. The practical bearings of this conclusion are obviously of the highest importance, lying as they do at the very root of many questions in regard to the factors of evolution, not to mention such practical ones as education and eugenics.

"While this viewpoint has been gradually gaining content and prevision, the science of heredity has been advancing not only by exact studies of the structure and physiology of the germ cells, but also by statistical investigations of the results of heredity—the various characters of animals and plants in parent and offspring." (Woodruff, "The Development of the Sciences," Chap. VI, pp. 248–249. Yale University Press, New Haven, 1923.)

Glucose (Dextrose). One of the two basic nutritive carbohydrates formed in photosynthesis; the other being fructose. Both are monosaccharides with the chemical formula $C_6H_{12}O_6$, but they differ in their molecular structure, that is, the arrangement of the atoms in the molecule. Glucose is also known as *dextrose* because, in solution, it turns the plane of polarized light to the right, while fructose under the same conditions turns the plane to the left and is therefore often designated as *levulose*. Glucose is widely distributed in the tissues of many plants. The digestion of the higher carbohydrates results in the formation of glucose (and fructose) which is the only carbohydrate available for energy.

Golgi Bodies, Golgi Apparatus. "By these various names are designated a group of cell-components, as yet imperfectly known, which show some points of resemblance to the chondriosomes though morphologically quite distinct from them. Like the chondriosomes the Golgi-elements are in considerable degree polymorphic, though always consisting, apparently, of the same specific material. . . .

"The Golgi apparatus is of very wide distribution among the cells of higher animals and is known in the Protozoa, everywhere showing the same general characters; and there is reason to believe that the same may be true of plant cells though considerable doubt concerning this still exists. It appears in two principal forms, the *localized* and the *diffuse*, which may be converted into one another in changing phases of cell-activity and are therefore to be regarded as merely different phases of the same structural element. In its localized form, as first described by Golgi ('98) in nerve-cells of the spinal

ganglia of vertebrates, it commonly gives the appearance of a localized net-like structure, composed of more or less contorted and varicose fibrils, which appear intensely black after silver impregnation or prolonged treatment by osmic acid. . . .

"Concerning the functional significance of the Golgi-elements even less is known than in case of the chondriosomes." (Wilson, "The Cell in Development and Heredity," pp. 48, 49, 52, The Macmillan Company, New York, 1925).

Harvey. The epoch-making work of Vesalius on anatomy was matched on the functional side in 1628 "with the publication of Harvey's tract, *Exercitatio Anatomica de Motu Cordis et Sanguinis in Animalibus.* No rational conception of the economy of the animal organism was possible under the influence of the Galenic system, and it remained for Harvey (1578–1657) to demonstrate by a series of experiments, logically planned and ingeniously executed, that the blood flows in a circle from heart back to heart again, and thus to supply the groundwork for a proper understanding of the dynamics of the organism as a whole. A new picture of the function of the blood was presented which quickly led to the discovery of the lymphatic system, and gave content to the study of the nutrition of the body.'

"Harvey's use of distinctively quantitative factors is so important in its establishment of the experimental method in biology that his own statement is of great historical interest:

"'I frequently and seriously bethought me, and long revolved in my mind, what might be the quantity of blood which was transmitted, in how short a time its passage might be effected, and the like; and not finding it possible that this could be supplied by the juices of the ingested aliment without the veins on the one hand becoming drained, and the arteries on the other hand getting ruptured through the excessive charge of blood, unless the blood should somehow find its way from the arteries into the veins, and so return to the right side of the heart; I began to think whether there might not be a motion, as it were, in a circle. Now this I afterwards found to be true; and I finally saw that the blood, forced by the action of the left ventricle into the arteries, was distributed to the body at large, and its several parts, in the same manner as it is sent through the lungs impelled by the right ventricle into the pulmonary artery, and that it then passed through the veins and along the vena cava, and so round to the left ventricle in the manner already indicated. Which motion we may be allowed to call circular.'" (Woodruff, "The Development of the Sciences," Chap. VI., pp. 224–225, Yale University Press, New Haven, Conn., 1923.)

Hippocrates. See Biology and Medicine.

Histology. "Histology is the science that treats of the minute structure of the tissues and organs of the plant and animal body. The study of the living cells lacks the factor of permanency of record, except in those instances where this has been accomplished by photographic methods. This difficulty and that of distinguishing the different parts of the cell in the living condition have been overcome to some extent by the study of cells and tissues which have been killed, that is, "fixed," and then stained in various ways. A study

of both living and fixed cells is necessary for knowing the structure and function of particular cells and tissues.

"The great mass of work done today in both normal and pathologic histology depends on the fixation of the tissues and their subsequent staining in an elective manner. All of the fixatives in use precipitate the proteins; many of them leave the lipins unaffected; but most of them remove the carbohydrates and many of the salts. Accordingly, to study all of these constituents of a cell, various fixation methods must be used.

"The next step in the preparation of fixed tissues for study consists in slicing them into very thin layers. This is usually accomplished by freezing a bit of tissue, after which it can be sectioned in a special instrument, or by infiltrating it with a solution of gelatin, paraffin, or celloidin which is later solidified so that the tissue and the embedding matrix may be sectioned together. The use of both paraffin and celloidin requires that the tissue shall be dehydrated in alcohol, which removes most of the lipins. The use of paraffin permits the tissues to be sectioned relatively rapidly and in very thin slices. Celloidin, on the other hand, disturbs the arrangement of the cells less and causes less shrinkage than does the paraffin method.

"These thin slices may be stained to demonstrate the various parts of the cell and the intercellular substance. The most usual staining method—hematoxylin and eosin—stains the nucleus blue and the cytoplasm pink. Special staining methods are necessary to demonstrate certain cellular constituents that are present in the dead cell body but are not made visible by hematoxylin and eosin. A host of such staining methods has been devised; a few are indispensable, but most of them are of questionable value." (Maximow and Bloom, "A Textbook of Histology," pp. 2–3, W. B. Saunders Company, Philadelphia, 1934.)

History of Biology. See Biology and Medicine.

Hooke, Robert (1635–1703). "Intellectually Robert Hooke was unquestionably the most distinguished of the classical microscopists. He was, however, primarily a physical experimenter, and most of his best work lies outside our field. Sickly from childhood, his health prevented him from receiving a normal education. He was, however, a precocious and rapid worker. At Oxford he attracted the attention of Robert Boyle. When the Royal Society was founded, he entered its service as a salaried 'curator of instruments.' This country has produced no more brilliant, ingenious, and inventive experimenter, and in certain important matters he anticipated Newton. He was a virulent and acrimonious controversialist, jealous and censorious beyond all tolerable limits, with a spirit warped by congenital infirmities of body and temper.

"Hooke's *Micrographia*, published in London in 1665, opens with a description and figure of his microscope. This account is a valuable landmark in the history of the subject. The book is made up of a number of observations. Their chief biological importance is in the accuracy and beauty of his figures, which formed a standard for generations. Biology is the loser from the application of his great intellect to other departments.

"Hooke has a figure of the microscopic structure of cork, showing the walls bounding the cells. He refers to these as *cells*. That word in our modern biological nomenclature comes from him." (Singer, "The Story of Living Things, p. 168, Harper & Brothers, New York, 1931.)

Hopkins, Frederick Gowland. *Feeding experiments illustrating the importance of accessory factors in normal dietaries.* The experiments described in this paper confirm the work of others in showing that animals cannot grow when fed upon so-called "synthetic" dietaries consisting of mixtures of pure proteins, fats, carbohydrates, and salts. But they show further that a substance or substances present in normal foodstuffs (for example, milk) can, when added to the dietary in astonishingly small amount, secure the utilization for growth of the protein and energy contained in such artificial mixtures. . . .

"Convinced of the importance of accurate diet factors by my own earlier observations, I ventured, in an address delivered in November, 1906, to make the following remarks:

"'But, further, no animal can live upon a mixture of pure protein, fat, and carbohydrate, and even when the necessary inorganic material is carefully supplied the animal still cannot flourish. The animal body is adjusted to live either upon plant tissues or the tissues of other animals, and these contain countless substances other than the proteins, carbohydrates, and fats. Physiological evolution, I believe, has made some of these well-nigh as essential as are the basal constituents of diet; lecithin, for instance, has been repeatedly shown to have a marked influence upon nutrition, and this just happens to be something already familiar, and a substance that happens to have been tried. The field is almost unexplored; only is it certain that there are many minor factors in all diets, of which the body takes account. In diseases such as rickets, and particularly in scurvy, we have had for long years knowledge of a dietetic factor; but though we know how to benefit these conditions empirically, the scale errors in the diet are to this day quite obscure. They are, however, certainly of the kind which comprises these minimal qualitative factors that I am considering. Scurvy and rickets are conditions so severe that they force themselves upon our attention; but many other nutritive errors affect the health of individuals to a degree most important to themselves, and some of them depend upon unsuspected dietetic factors.'" . . .

"Evidence has now accumulated from various sides to justify these views. That a deficiency in quite other factors can induce disease is a fact which is now upon a firm experimental basis. That a deficiency, quite as little related to energy supply, may result in the failure of so fundamental a phenomenon as growth in young animals seems equally certain." (Fulton, "Selected Readings in the History of Physiology," pp. 299–301, Courtesy of Charles C. Thomas, Springfield, Ill., 1930.)

Hormones—Historical. "Organ magic has figured in the folk superstitions of many peoples. A primitive form of the belief is that man can increase the store of his own virtues by consuming various organs of his fellow man or of animals taken in the chase. The warrior eats the heart of his enemy to add to his own courage. As early as the beginning of the Christian era the

practice in a less naïve form had come under the sanction of orthodox medicine. Diseases of one sort or another were believed to be due to the lack of mysterious substances supplied to the body as a whole by different individual organs; it followed that the resulting diseases were to be cured by supplying artificially these lacking substances. As a system of treatment this came ultimately to be known as *opotherapy.* It was employed systematically by Celsus and Dioscorides. Wolf's liver was prescribed for diseases of that organ, hare's brain for nervousness, and fox's lung for respiratory disorders. Throughout the ages, sex gland material has been given as an antidote for loss of virility. As Paracelsus phrased the doctrine, 'heart cures heart, spleen spleen, lungs lungs.'

"During the Middle Ages in Europe a large number of revolting organic substances came into standard use in the treatment of diseases. The ingredients of the witches' brew listed in *Macbeth* may serve as a fair sample of these, though even more disgusting materials were actually used. Altgether, they made up the 'filth pharmacopeias.'

"It is historically interesting that modern medical interest in the internal secretions grew out of the ancient practice of opotherapy. Brown-Séquard was a French physiologist who was at one time a professor at Harvard University. Later he established himself in Paris where he carried out a series of brilliant researches. Toward the end of his life he was overtaken by general debility while many interesting things remained yet to be done. He was led to treat himself by injections of extract of sex glands. The experiments were reported before the Société de Biologie of Paris on May 31, 1889—a date that is sometimes cited as 'the birthday of endocrinology.' So eminent was the scientist and so spectacular the beneficial results he claimed to have experienced that world-wide interest was immediately aroused. The very meagre stream of contributions that up to this time had been devoted to the science of endocrinology soon was swollen to a flood.

"Whether Brown-Séquard's results were more than a triumph of suggestive therapy is doubtful. But growing out of his error, if error it was, has come a development in the field of medicine more significant than any other since the discovery of the bacterial origin of disease. The evidence is now conclusive that what we are—physically, mentally, sexually and emotionally—depends in no small measure upon the functions of our endocrine glands. They coöperate in an important way in the regulation of our activities in health, and modify the course when they do not primarily determine our diseases. A fundamental new principle has been added to physiology.

"In a fascinating account of the history of the endocrine doctrine, Garrison points out that the first clearly to state the function of the internal secretions was the fashionable physician at the Court of Louis the Fifteenth, Theophile de Bordeu. Of him, Garrison writes: 'It was his ambition to confirm and uphold the humoral pathology of Hippocrates. . . . Bordeu's slender reputation today is centered in a single idea—the doctrine that not only each gland, but each organ of the body, is the workshop of a specific substance or secretion which passes into the blood and that upon these secretions the physiological

integration of the body as a whole depends.'" (Hoskins, "The Tides of Life," pp. 15–17, W. W. Norton & Company, Inc., New York, 1933.)

Hydra. "The body of Hydra somewhat resembles a long narrow sac, the base constituting the FOOT, and the opening at the opposite end forming the MOUTH. Surrounding the mouth is a circle of out-pocketings of the body wall termed TENTACLES. The main axis of the body extends from foot to mouth, and every plane passing through this axis divides the body into symmetrical halves. In other words, the parts of the body are symmetrically disposed about, or radiate from the main axis, and so Hydra affords an example of RADIAL SYMMETRY.

"The body wall of Hydra is composed of two distinct cell layers, ectoderm and endoderm, separated by a thin non-cellular supporting layer of jelly-like material (MESOGLOEA) secreted by the cells of both ectoderm and endoderm. Hydra thus illustrates a simple type of metazoan structure in which but two primary tissues exist; such specializations as are necessary for the performance of the essential life functions being confined to the various cells that compose these layers. The majority of the cells of the endoderm which line the ENTERIC CAVITY are concerned with the digestion of solid food taken in through the mouth, while those of the ectoderm are variously modified for protection, and the other relations of the individual to its surroundings, as well as for reproduction.

"In short, in the organization of Hydra the *primary* tissues (ectoderm and endoderm) have not become differentiated into *secondary* specialized tissues (muscular tissue, nerve tissue, etc.) for one function or another—the simple life processes of the animal are adequately provided for by the specialization of isolated cells or small groups within ectoderm and endoderm." (Woodruff, "Foundations of Biology," pp. 104–105, The Macmillan Company, New York, 1936.)

Hydrogen Ion. "The reaction of a solution, that is, the degree of its acidity or alkalinity, depends only upon the relative concentrations of the electropositive hydrogen ion (H^+) and the electronegative hydroxyl ion (OH^-) in the solution. An excess of hydrogen ions causes an acid reaction; an excess of hydroxyl ions causes an alkaline reaction. If the concentration of the hydrogen ions equals the concentration of the hydroxyl ions, the solution is said to be *neutral.* Water molecules on dissociation furnish an equal number of hydrogen and hydroxyl ions, and water is neutral in reaction. The number of water molecules that dissociate electrolytically (ionize) is very small. At 22°C., only 0.0000001 per cent of the water molecules are ionized, and this is the reason why pure water does not conduct a measurable electric current. The extent of ionization on part of an acid or alkali added to water determines the degree of acidity or alkalinity of the resulting solution. Any excess of acid or base added to water represses the ionization on part of the water, and the product of the concentrations of the two ions remains a constant. The acidity or alkalinity, that is, the reaction of a solution, therefore can be expressed in terms of either of these two ions. Knowing the concentration of hydrogen ions, the concentration of hydroxyl ions is likewise given. The

concentration of hydrogen ions can be determined with far greater accuracy and ease than the concentration of hydroxyl ions, and the reaction of a solution therefore is usually stated in terms of hydrogen ion concentration.

"In biological fluids, the concentrations of hydrogen ions and hydroxyl ions are of the order of water; they are extremely small. On that account, the reaction of a biological fluid is best stated by the method designated as the pH of the solution. The pH expresses the reciprocal value of the hydrogen ion concentration in grams per liter in logarithmic notation. That is to say the pH equals 1/cH expressed as its logarithm. It is evident that in this manner one obtains, instead of a minute decimal fraction, a large whole number. It must be remembered that the lower the pH the higher the concentration of hydrogen ion in the solution, and vice versa.

"The blood and tissue fluids are almost neutral in reaction, and the variations in acidity (or alkalinity) consistent with life are extremely small. Of all the body fluids, the pH of the arterial blood plasma normally varies from 7.42, while the body is at rest, to 7.35, while the body is at work. This corresponds to a variation of 0.00000007 g. of hydrogen ion concentration in 1 liter of blood plasma. The variations of the pH in the venous blood plasma lie between 7.39 and 7.28. The pH of the blood plasma of a comatose diabetic patient, dying of acidosis, may be lowered to pH 7.00. If the alkalinity of the blood is increased and the pH of the blood plasma is raised to 7.60, tetanic spasms occur. The range of the pH of the blood plasma, compatible with life, may be said to lie between pH 7.00 and pH 7.70. In terms of hydrogen concentration, this amounts to a variation of about five ten-millionths of a gram of hydrogen ions in the total volume of the blood of an adult human being of average height.

"The average pH of the lymph exceeds that of the blood plasma by about 0.05 units. Lymph, therefore, is slightly more alkaline. The variations in pH of the different fluids secreted and excreted by the body cells are greater. Pancreatic juice has an average pH of 8.3. It is much more alkaline than the blood or tissue fluid. The pH of the saliva is about 6.8; that is say, saliva is slightly acid. The pH of the urine varies during the day from pH 5.00 to pH 7.00 with an average pH for the 24-hour urine of about pH 6.00. The gastric juice is extremely acid; its pH varies between 0.90 to 1.60. The maintenance of the physiological neutrality of blood and tissue fluid, therefore, is a constant battle with disturbing factors that tend to shift the reaction from its physiological level. One of the main mechanisms whereby the blood and tissue fluids maintain the physiological reaction is the buffer action of certain salts. (Eulenburg-Wiener, "Fearfully and Wonderfully Made," pp. 216–218. The Macmillan Company, New York, 1938.) See Dissociation.

Infusoria. See Protozoa; Paramecium.

Insecta. See Arthropoda.

Interstitial Cells. 1. "The testis, besides producing spermia, causes the development and maintenance of the so-called 'secondary sexual characters' and of the sex impulse. In the developing organisms it is supposed to regulate the growth of the skeleton and of other parts. After excision of both testes

in the prepubertal age, the normal cessation of the growth period of the long bones of the extremities is delayed, and the secondary sexual characters do not develop. If this is done after puberty, the libido gradually disappears, the secondary sexual characters and the auxiliary sex glands undergo partial involution, and disorders of metabolism eventually appear, as obesity, etc. The implantation of a testis into such an individual may restore normal conditions to a certain extent. In experimental animals the injection of testicular hormone prevents many of these changes from occurring.

"Experiments on animals have shown that implantation of a testis may cause the appearance of secondary male characters even in a spayed female. This is due to a hormone secreted by the testis. Some authors ascribe the production of this hormone to the interstitial cells; others, to the seminiferous epithelium (spermatogenic and Sertoli cells). A third possibility is, of course, the participation of both elements.

"Most of the data favor the first hypothesis. It is known that individuals with cryptorchid testes display, in most cases, a normal sexual behavior and normal secondary characters; they usually retain their virility, although sterility is the rule. The seminiferous tubules in the testes of such males are always atrophic, as a result of the higher temperature in the abdomen. In experimental animals with cryptorchid testes of long duration, the seminiferous tubules seem to disappear completely, leaving large masses of interstitial cells. Such individuals, as a rule, keep their libido, the potentia coeundi, and the secondary sexual characters. Similar results were obtained after ligation of the vas deferens or the ductuli efferentes and after large doses of x-rays. Grafts of testicular tissue into castrated animals are supposed to act through their interstitial cells, which proliferate, while the seminiferous tubules become atrophic. These and many other facts indicate that the male sexual hormone is very probably secreted by the interstitial cells rather than the seminiferous epithelium."

2. "Much has been written on the endocrine nature of the 'interstitial cells' of the ovary. Recent investigations have shown that they do not play any particular role as endocrine elements in influencing the secondary sexual characters or in regulating the sexual cycle. It is impossible to separate them experimentally from the other constituents of the ovary and to test their physiologic importance. It is possible that they have something to do with the nutrition of the follicles and perhaps also of the corpora lutea." (Maximow and Bloom, "A Textbook of Histology," pp. 507, 539, W. B. Saunders Company, Philadelphia, 1934.)

Intracellular. The term refers to the materials contained within the boundary of each cell or to vital phenomena occurring within the cell as, for example, intracellular movements (*cyclosis*). Some authorities hold that all tissue materials, whether intercellular or intracellular, are living, but the more common conception is that protoplasm is intracellular, that is, occurs within the cell boundary. On this conception, such intercellular materials as the *collagenous* intercellular tissues of the connective tissues and blood plasma are nonliving substances secreted by the intracellular protoplasm.

In a resting cell, cytoplasm and nucleus are seen as the primary intracellular units of protoplasm, and each contains numerous formed bodies. Included in the cytoplasm are *chondriosomes*, *Golgi bodies*, *plastids*, *centrosome*, *metaplasm* (ergastic substance), and cell vacuoles. In the nucleus is the nucleolus, chromatin, and the nuclear protoplasm.

Ions. See Dissociation; Hydrogen Ion.

Keratin. "Keratin is a nitrogenous organic substance which may be formed by epithelial cells. It is the basis of *horny* structures. Its most characteristic development is seen in the epidermis of vertebrates. Produced within the cell, the keratin is deposited in the peripheral region of the cell and at the expense of the cytoplasm. As the process reaches its limit, the nucleus and remnant of cytoplasm die and dry up. What was a living cell is then merely a minute horny scale—in contrast to the fact that cells which produce a cuticula remain alive. As the keratin is deposited, adjacent cells somehow become strongly adherent so that the entire keratinized or 'horny' layer (*stratum corneum*) acquires a high degree of mechanical resistance. The process may involve only the outermost tier of cells of the epidermis, as in some amphibians, or, as in reptiles, several or many of the upper layers of cells become horny. On the human body the stratum corneum varies from a thin and flexible layer, as on the back of the hand, to a thick hard and tough layer, as in the callosities of the palm and sole.

"The stratum corneum is one of the most important epithelial products of a vertebrate. Fishes have merely a cuticular outer layer on the epidermis. Apparently amphibians introduced the stratum corneum. The characteristic superficial scales of reptiles and feathers, hair, claws, hoofs, nails, and the hollow horns of ruminant ungulates are all differentiations of the stratum corneum—they are epithelial products.

"In amphibians and reptiles the horny layer is shed periodically and either entire or in large fragments. In birds and mammals minute particles of the layer are constantly sloughing off. The material thus lost is replaced by growth in the deeper part of the epidermis. In animals which shed periodically, a new horny layer is well established beneath the old before the old is shed. The animal therefore passes through no such critical period as the 'soft-shelled' stage of a crab. It is this ease of repair and replacement of the outermost layer of the body which makes the stratum corneum incomparably superior to a cuticular layer for the uses of large heavy land animals." (Neal and Rand, "Comparative Anatomy," p. 135, Copyright P. Blakiston's Son & Company, Philadelphia, 1936.)

Lactation. See Mammary Glands.

Lacteals. See Lymph.

Lactose (Milk Sugar). "Lactose occurs in milk and is made commercially from the whey of milk used in the manufacture of cheese or casein. In the body lactose is digested into equal parts of glucose and galactose, the nutritive functions of which have been noted above. Lactose has special interest for the student of nutrition for at least two reasons. It is not found

in the blood or body tissues generally, but is evidently formed only in the mammary gland for secretion in the milk, which suggests its especial importance in the nourishment of the young. It also appears to be unique among the sugars in its property of favoring the development of the most desirable species of bacteria in the intestine." (Sherman, "Food Products," pp. 9–10, The Macmillan Company, New York, 1926.)

Lamarck. See Organic Evolution.

Linnaeus. See Taxonomy.

Malaria. See Plasmodium.

Malpighi. "The versatility as well as the genius of Malpighi (1628–1694) is illustrated by his studies on the anatomy of plants, the function of leaves, the development of the plant embryo, the embryology of the chick, the anatomy of the silkworm, the structure of glands. Master of morphology but with prime interest in physiology, his lasting contribution lies in his dependence on the microscope for the elucidation of problems where structure and function, so to speak, merge. This is well illustrated by his ocular demonstration of the capillary circulation in the lungs, at once his first and greatest discovery and the first of prime importance ever made with a microscope—since it completed Harvey's work on the circulation of the blood. Malpighi wrote: 'I see with my own eyes a truly great thing. . . . It is clear to the senses that the blood flowed away along tortuous vessels and was not poured into spaces, but was always contained within tubules, and that its dispersion is due to the multiple winding of the vessels.'" (Woodruff, The Development of the Sciences," Chap. VI, p. 229, Yale University Press, New Haven, 1923.)

Maltose. "Maltose occurs in malted or germinated grains, in malt extracts, etc., but the amount of maltose eaten as such is not likely to be large. It is formed in quantity by the digestion of starch by the saliva or the pancreatic juice. Maltose, however, whether eaten or formed in the course of digestion, is not absorbed as such to any important extent, but is split by a digestive ferment of the intestinal juice, each molecule of maltose yielding two molecules of glucose." (Sherman, "Food Products," p. 10, The Macmillan Company, New York, 1926.)

Mammary Glands. "The mammary glands for several years after birth remain small, and alike in both sexes. Towards puberty under the stimulus of the newly-present sex hormones they begin to enlarge in the female, and when fully developed form in that sex two rounded eminences, the *breasts*, placed on the thorax. A little below the center of each projects a small eminence, the *nipple*, and the skin around this forms a colored circle, the *areola*. In virgins the areolae are pink; they darken in tint and enlarge during the first pregnancy and never quite regain their original hue. The mammary glands are constructed on the compound racemose type. Each consists of from fifteen to twenty distinct lobes, made up of smaller divisions; from each main lobe a separate *galactophorous* duct, made by the union of smaller branches from the lobules, runs towards the nipple, all converging beneath

the areola. There each dilates and forms a small elongated reservoir in which the milk may temporarily collect. Beyond this the ducts narrow again, and each continues to a separate opening on the nipple. Imbedding and enveloping the lobes of the gland is a quantity of firm adipose tissue which gives the whole breast its rounded form.

"During maidenhood the glandular tissue remains imperfectly developed and dormant. Early in pregnancy it begins to increase in bulk; this secondary development being due to stimulation by lutein, secreted by the persistent corpus luteum of pregnancy; and the gland-lobes can be felt as hard masses through the superajacent skin and fat. Even at parturition, however, their functional activity is not fully established. The mammary glands are modified sebaceous glands. The oil-globules of the milk are formed by a sort of fatty degeneration of the gland-cells, which finally fall to pieces; the cream is thus set free in the watery and albuminous secretion formed simultaneously, while newly developed gland-cells take the place of those partially destroyed. In the milk first secreted after accouchement (the *colostrum*) many cells float in the liquid, which has a yellowish color; this first milk acts as a purgative on the infant, and probably thus serves a useful purpose, as a certain amount of substances (biliary and other), excreted by its organs during development, are found in the intestines at birth." (Martin, "The Human Body," pp. 631–632, Henry Holt & Company, New York, 1935.)

Matter, Structure of. "For more than 2,500 years, men interested in metaphysics have speculated concerning the ultimate constitution of matter. Ancient Hindu and Greek philosophers held that the physical universe (or, as sometimes taught, the whole universe, both physical and mental) is composed of very small indivisible particles, or atoms, that are in constant motion. The first clear statements of this idea came in the writings of Leucippus and Democritus, who taught that all phenomena are to be explained by the incessant movements of atoms, which differ only in shape, order, and position.

"The beginnings of a scientific understanding of the structure of matter date back only to the work of Lomonosov, a Russian physical chemist (1743), and to that of John Dalton, an Englishman (1803–1807) who has given to us the basis of the modern atomic theory. The Russian work was to all practical purposes buried and unknown and was resurrected only in 1904. Dalton's work has played a most important part in correlating and interpreting the known facts of chemistry. Dalton states that all material substances are composed of minute particles or atoms of a comparatively small number of kinds. All the atoms of the same kind have the same size, weight, and other properties.

"The theory, as at first stated, has been developed, added to, and modified by the work of many investigators. During recent years, a very great amount of scientific evidence has been published of such a character as to establish beyond any reasonable doubt the facts of the atomic and molecular structure of matter. It is impossible here to trace the steps in the development of this bit of scientific truth; we can merely make a very simple and brief statement of the facts as they are known at the present time.

"Probably the most important addition to our information as to the structure of matter is the idea that the atom is not a simple indivisible thing. It has been shown to be a very complex system, whose components, subatoms or electrons, are in very rapid orbital motion. The electrons are of two kinds, positive and negative. These are alike in the strength of the electrical charge that they bear but wholly different in mass. The negative electron is associated with a mass that is 1/1,845 that of the hydrogen, the lightest known, atom. The diameters of some of these atoms have been calculated and found to be: for helium, 2×10^{-8} cm.; for the hydrogen atom, slightly less; and for oxygen and nitrogen atoms, slightly more. Sir Ernest Rutherford suggested the theory that the atom is constructed somewhat upon the plan of a solar system, having at its center a nucleus bearing positive electrical charges and negative electrons whirling in orbits about it. The rate of movement of these negative electrons appears to approach closely that of light. The electronic constituents are as small in comparison with the dimensions of the atomic systems as are the sun and planets in comparison with the dimensions of the solar system. Of course, in such a system, the electronic or other particles can occupy but a very small portion of the space enclosed within the system.

"As concerns the structure of matter, physicists have experienced rapidly changing thought in recent years. They now claim the existence of four, at least, instead of two kinds of elementary particles. These are

"1. *Electrons.* Units of electricity negatively charged and considered to form the 'outer shell' of atoms or to revolve about atomic hearts, or nuclei, like satellites about a sun. These have many of the properties of light and partake of the nature of a wave motion.

"2. *Protons.* Positive particles or corpuscles, the nuclei, or hearts, of hydrogen atoms. The mass of the proton is approximately 1,850 times that of the electron.

"3. *Neutrons.* Neutral particles of matter, consisting of a close combination of electron and proton, whose electrical charges neutralize each other.

"4. *Positive Electrons, Positrons.* Positively charged particles or corpuscles or rays discovered in cosmic rays. They have the mass of electrons but the opposite electrical charge." (Rogers, "Textbook of Comparative Physiology," pp. 6–7, McGraw-Hill Book Company, Inc., New York, 1938.)

Measurements. "In order better to grasp the dimensions that characterize the colloidal state, it will be well to stop a moment and recall the ultramicroscopic scale. A micron is one-millionth of a meter, or one-thousandth of a millimeter, and has the symbol μ. This unit does for microscopic objects; thus, a human blood corpuscle or an average globule of butterfat in milk is 8 μ across, and a bacterium is between 1 μ and 5 μ long. Ultramicroscopic particles require a smaller scale, such as was developed for measuring the wave length of light. The physicist uses the symbol mμ, the so-called millimicron, for the thousandth part of a millionth part of a meter. He also uses the symbol $\mu\mu$ to indicate the millionth part of a millionth part of a meter, the so-called micromicron.

"It is impossible to grasp the true size of such minute dimensions, but some idea of them can be gained if we approach them from objects of appreciable size. The following table may help to do this:

1 meter (m.) = 1,000 millimeters............	Sound waves are 16 to 17 mm. in length
1 millimeter (mm.) = 1,000 microns..........	Cells range from 0.15 mm. to 1 μ
1 micron (μ) = 1,000 millimicrons............	Colloidal particles range between 0.1 μ and 1 mμ
1 millimicron (mμ) = 1,000 micromicrons ($\mu\mu$).	Molecules range from 2.5 mμ (protein) to 46 $\mu\mu$ (water) and less

"To this scale, each member of which is a thousand times the one below it, may be added the Angstrom unit, A.U., used chiefly in indicating the wave length of light. It is 0.1 mμ and therefore 100 $\mu\mu$. The light waves of the visible spectrum are 7,500 A.U. long at the red end and 3,900 A.U. long at the violet end." (Seifriz, "Protoplasm," pp. 99–100, McGraw-Hill Book Company, Inc., New York, 1936.)

Mendel. "The first studies of this type which attracted the attention of biologists were made by Galton (1822–1911), who in the eighties and nineties of the last century amassed a large amount of data in regard, for example, to the stature of children with reference to that of their parents, and formulated his well-known 'laws' of inheritance. But the epoch-making work which eventually created the science of genetics was that of an Austrian monk, Gregor Mendel (1822–1884), who combined in a masterly manner the experimental breeding of pedigree strains of plants and the statistical treatment of the data thus secured in regard to the inheritance of sharply contrasting characters, such as the flower color in sweet peas. Mendel's work was published in 1865 in an obscure natural history periodical and he himself abandoned his teaching and research to become the abbot of his monastery. Thus terminated prematurely the scientific work of one of the epoch makers of biology, and the now famous 'Mendelian laws' of inheritance were unknown to science until 1900 when other biologists, coming to similar results, unearthed his forty-year-old paper. We can pause only to say that the fundamental principle of the segregation of the genes of the 'alternative' characters within the germ cells, which Mendel's work indicated, has been extended to other plants and to animals, and from being, as at first thought, a principle of rather limited application, now seems to be the key to all inheritance. And the present results are extremely convincing because cytological studies on the architecture of the chromosome-complex of the germ cells keep pace and afford a picture of the physical basis—of the mechanism by which the segregation and distribution of genes by the Mendelian formula takes place." (Woodruff, "The Development of the Sciences," Chap. VI., pp. 249–250, Yale University Press, New Haven, Conn., 1923.)

Metazoa. "The group Metazoa includes all animals above Protozoa and therefore has the rank of a subkingdom. On this basis Protozoa is both a

subkingdom and a phylum. The general features that distinguish Metazoa from Protozoa are as follows:

"1. The body of the Metazoan is composed of many cells that may be divided into two general classes: somatic cells and germ cells.

"2. The somatic cells are differentiated into tissues and organs, in which there is specialization of structure and function.

"3. The germ cells are the reproductive cells, which in many forms are segregated from the somatic cells early in ontogeny.

"4. Though asexual reproduction by fission or budding occurs, there is always sexual reproduction from a fertilized egg or, less commonly, an unfertilized egg.

"5. The developing egg undergoes cleavage; the cells or blastomeres thus formed adhere to one another to produce a multicellular complex.

"6. At least two germ layers develop: an ectoderm, forming the external covering, and an endoderm, lining the alimentary canal and its outgrowths. Between these, in the majority of metazoans, a third germ layer, the mesoderm, is formed from which muscles, vascular and other tissues and organs develop.

"The distinction between Metazoa and Protozoa is not sharp since colonial protozoans, such as Volvox, consist of groups of different kinds of cells, organically connected with one another. Colonial Protozoa to a certain extent bridge the gap between solitary Protozoa and Metazoa, but in the latter there is a greater degree of interdependence among the cells of the individual organism than there is between the individual members of a protozoan colony." (Wieman, "General Zoology," pp. 384–385, McGraw-Hill Book Company, Inc., New York, 1938.) See Protozoa.

Microscope, Development of. "The microbiologist is able to see these minute forms only by the help of the compound microscope, but some of them are too small even for its magnifications, and reliance must be placed on the ultramicroscope and filters to determine their presence, size, and form.

Since all of these organisms have to be studied by the help of the microscope, the advance of microbiology has been practically a history of the microscope. Whether the Dutch lens grinder, Jannsen, discovered the principle of the compound microscope or it was an Italian invention, the improvements that were made about the beginning of the seventeenth century were by a number of workers. Simple lenses and their properties had been known to the Romans, but the compound microscope with its magnification of 50 to 3,000 diameters opened a new world which amateur lens makers explored, as amateurs today spend their time with radio or electrical contrivances. A training in lens grinding preceded any examination of this new and fascinating region, but some amateurs became so skillful in grinding lenses accurately that they produced microscopes with a magnification of 300 or 400 diameters. The high-power lens on the ordinary student instrument of today gives a magnification of 400 to 500 diameters, so that these homemade instruments were real compound microscopes. They were ground, however, to no fixed formula as to the shape and glass. A modern lens is not an instru-

ment that is made and improved by progressive trials but is ground to an exact curvature from glass with known exact refractive index and dispersion. With these primitive instruments, however, one enthusiastic amateur was able to see bacteria. Leeuwenhoek, a Delft Dutchman (1632–1723), drew them with an accuracy and skill that would be a credit to a student equipped with a much better outfit. On Sept. 14, 1683, he communicated his discovery in a letter to the Royal Society of London.

"It is interesting to note that, although Leeuwenhoek discovered bacteria in 1683, Linnaeus, the great Swedish botanist, when writing a systematic account of the plant kingdom, named and classified a few of the larger fleshy fungi and then grouped all the other small, unknown, and undescribed plants into the great order of 'Chaos.'

"The bacteria continued to be studied by such lenses as were available during the eighteenth and nineteenth centuries, and the botanists who specialized in bacteria laid the foundations for our modern classification. About fifty years ago (1879), the microscope was further improved by the homogeneous oil immersion objectives, and magnifications up to 1,000 diameters could be obtained. The very smallest living organisms could be studied with greater ease when they were placed under such relatively high powers. This principle was not a new one, for water had been used as a substitute for the air intervening between objective and cover glass by Amici in 1840 and Hartnack in 1855, glycerin by Gundlach in 1867, and various oils by Amici in 1869. The new principle was to use an oil that had approximately the same refractive index as glass, cedar oil most nearly answering this requirement.

"In 1886, a still further improvement in the lenses was made by the invention of apochromatic objectives with compensating oculars. These apochromatic oil-immersion objectives, made up of at least eight different lenses, were so perfect that a magnification of about 3,000 diameters was possible. This improvement was due to Ernst Abbe, a physics professor in the University of Jena, so of whatever laurels bacteriology and cytology have gathered in the past 50 years a large part must be laid at the feet of the man who has given microbiology the tools with which to work. Today, the bacteria and even many details inside them, in spite of their almost incredible smallness, can be seen. This advance was made possible by the invention of the new types of glass which had different refractive indexes and dispersions from the old crown and flint glasses which were all that lens makers had formerly at their disposal. Otto Schott, a practical glassmaker and chemist, found that, by adding the proper chemicals, baryta, borate, phosphate, and zinc, glasses could be produced that had very different properties from the flint and crown glasses. By combining some of these glasses, Abbe was able to build up a lens that produced an image that was not only color free, achromatic, but that had extraordinary definition and freedom from distortion.

"These high-power objectives are smaller than the head of an ordinary brass pin so that they could not have been used, if, at the same time, some system of concentrating the light had not been invented. We owe to Abbe the illuminating apparatus, or condenser, which furnishes better illumination

and a better microscopic image." This was invented in 1872. (Lutman, "Microbiology," pp. 8–10, McGraw-Hill Book Company, Inc., New York, 1929.)

Milk. "Milk contains at least two proteins, *lactalbumin* and *casein;* several fats in the *butter;* a carbohydrate, *milk sugar* or *lactose;* much water; and salts, especially potassium and calcium phosphates. *Butter* consists mainly of the same fats as those in beef and mutton but has in it about 1 per cent of a special fat, butyrin. In the milk, the fat is disseminated in the form of minute globules which, for the most part, float up to the top when the milk is let stand and then form the *cream.* In this, each fat droplet is surrounded by a pellicle of albuminous matter; by churning, these pellicles are broken up and the fat droplets then run together to form the butter. Milk is also rich in vitamins; the presence of vitamins in milk and eggs is obviously essential for the proper growth and development of mammals and birds, respectively, during the early periods of life.

"Casein is insoluble in water, but when acted on by *rennin,* an enzyme of gastric juice, is converted into *paracasein,* which forms an insoluble compound with the lime salts of the milk, and so is precipitated as the *curd.* Casein itself is rendered insoluble by acid; when milk is kept, its sugar ferments, giving rise to lactic acid, the familiar process of souring; after this reaches a certain point the casein is precipitated as 'clabber.' There is sufficient difference between the two forms of curd so that cheeses made from them are quite unlike; cottage cheese, made from sour milk, cannot be 'ripened' as can cheese made from milk acted upon by 'rennet' in the ordinary commercial process of cheese making.

"Human milk is undoubtedly the best food for an infant in the early months of life; and to suckle her child is useful to the mother if she be a healthy woman. Many women refuse to suckle their children from a belief that so doing will injure their personal appearance, but skilled medical opinion is to the contrary effect; the natural course of events is the best for this purpose, unless lactation be too prolonged. Of course in many cases there are justifiable grounds for a mother's not undertaking this part of her duties; a physician is the proper person to decide." (Martin, "The Human Body," pp. 472–473, 632, Henry Holt & Company, New York, 1935.)

Mucous Membrane. "The skin can be readily enough removed from all parts of the exterior, but at the margins of the apertures of the body it seems to stop, and to be replaced by a layer which is much redder, more sensitive, bleeds more readily, and which keeps itself continually moist by giving out a more or less tenacious fluid, called *mucus.* Hence, at these apertures, the skin is said to stop, and to be replaced by *mucous membrane,* which lines all those interior cavities, such as the alimentary canal, into which the apertures open. But, in truth, the skin does not really come to an end at these points, but is directly continued into the mucous membrane, which last is simply an integument of greater delicacy, but consisting fundamentally of the same two layers—a deep, fibrous layer, containing blood-vessels, and a superficial bloodless one, now called the *epithelium.* Thus every part of the body might

be said to be contained between the walls of a double bag, formed by the epidermis, which invests the outside of the body, and the epithelium, its continuation, which lines the alimentary canal." (Huxley, "Lessons in Elementary Physiology," p. 12, The Macmillan Company, New York, 1918.)

Nucleolus. "Nearly all metabolic nuclei contain one or more *true nucleoli*, or *plasmosomes*. In a young nucleus just formed by division there are often several small nucleoli which may unite to form two or one as the nucleus becomes fully developed. In the living nucleus the nucleolus appears as a dull, viscous droplet, usually round but frequently irregular in shape. Centrifuging and the position it naturally assumes in certain eggs show it to be heavier than the rest of the nuclear matter. It may be homogeneous throughout, or it may contain vacuole-like masses and occasionally small granules. Chemically, it is composed mainly of proteins and lipides. It commonly shows an affinity for acid dyes, but in some procedures it takes the basic ones. Of greater interest is the fact that its chromaticity undergoes marked alterations during the nuclear division cycle. . . . Such alterations are thought to indicate interactions of some sort with the reticulum, with which the nucleolus is in contact at one or more points. . . .

"The functions of the nucleolus are obscure, but there is obviously some relation between its behavior and the cycle of alterations undergone by the other nuclear constituents. . . . It should, however, be pointed out here that the nucleolar matter arising in the young nucleus develops principally in close association with definitely localized regions of particular chromosomes, a fact which has only recently come to light. The nucleolus or nucleoli tend to remain attached to such chromosomes and consequently to the metabolic reticulum which the latter form. As the reticulum again develops condensed chromosomes, the nucleolar matter diminishes in amount and commonly disappears completely. This long ago suggested that it is with the chromosomal changes especially that the nucleolus is concerned." (Sharp, "Introduction to Cytology," pp. 57–58, McGraw-Hill Book Company, Inc., New York, 1934.)

Organic Evolution. "Since we have every reason to believe that all life now arises from pre-existing life and has done so since matter first assumed the living state, it apparently follows that the stream of life is continuous from the remote geological past to the present and that all organisms of today have an ancient pedigree. This leads up to a question which has interested and perplexed thinking men of all times: how things came to be as they are today. It was the Greek natural philosophers who projected the idea of history into science and attempted to substitute a naturalistic explanation of the earth and its inhabitants for the established theogenies, and thus started the uniformitarian trend of thought which culminated in the establishment of organic evolution during the past century.

"Again it is Aristotle who is singled out among the Greeks for his combination of sound philosophy and induction which reaches no higher expression than in his statements regarding the relationships of organisms. He says, in substance: Although the line of demarcation is broadly defined, yet

nature passes by ascending steps from one to the other. The first step is that of plants; which, compared to animals, seem inanimate. The second step nature takes is from plants to plant-animals, the zoophytes. The third step is the development of animals, which arise from an increased activity of the vital principle, resulting in sensibility; and with sensibility, desire; and with desire, locomotion. Man is the head of animal creation. To him belongs the God-like nature. He is pre-eminent by thought and volition. But although all are dwarf-like and incomplete in comparison with man, he is only the highest point of one continuous ascent.

"Broadly speaking, Aristotle apparently held substantially the modern idea of the evolution of life from a primordial mass of living matter to the highest forms, and believed that evolution is still going on—the highest has not yet been attained. In looking for the effective cause of evolution Aristotle rejected Empedocles' hypothesis of the chance play of forces, which embodied in crude form the idea of the survival of the fittest, and substituted secondary natural laws to account for the fact that 'Nature produces those things which, being continually moved by a certain principle contained in themselves, arrive at a certain end.' Aristotle's rejection of the hypothesis of the survival of the fittest to account for adaptations of organisms was a sound induction from his necessarily limited knowledge of nature—but had he accepted it he would have been the 'literal prophet of Darwinism.'

"Although the thread of continuity of evolutionary thought is not broken from Aristotle to the present, no historical interest will be served in following . . . the Renaissance naturalists and speculative evolutionists, who, with a minimum of fact and a plethora of imagination were the worst enemies of the evolution idea. In truth, the great natural philosophers from Bacon and Leibnitz to Kant and Hegel laid the broad foundation for our modern attack on evolution, but from the strictly biological viewpoint, two Frenchmen, Buffon and Lamarck, and two Englishmen, Erasmus Darwin and his grandson, Charles Darwin, stand pre-eminent—and the greatest is Charles Darwin.

"Buffon (1707–1788) was a peculiarly happy combination of popular writer and scientist—entertaining by each new volume of his great *Histoire Naturelle* the social set of Paris, and instructing them at the same time. And it was largely between the lines of his Natural History that Buffon's evolutionary ideas found expression: but expressed they were, though sometimes difficult to decipher—beyond the ken, Buffon hoped, of the censor and dilettante, for apparently he was not of martyr stuff. It is not strange, therefore, that there are some differences of opinion amongst biologists today as to just how much weight is to be placed on some of Buffon's statements, but certainly it is not exaggerating to ascribe to him not only the recognition of the factors of geographical isolation, struggle for existence, artificial and natural selection in the origin of species, but also, which is equally important, the propounding of a theory of the origin of variations. He thought that the direct action of the environment brings about modifications of the structure of animals and plants and these are transmitted to the offspring.

"When Buffon's influence was at its zenith, Erasmus Darwin (1731–1802), a successful medical practitioner, expressed consistent views on the evolution of organisms in several volumes of prose and poetry. Although a contemporary critic in the *Edinburgh Review* remarked that Darwin's 'reveries in science have probably no other chance of being saved from oblivion, but by having been married to immortal verse,' today biologists recognize him as the anticipator of Lamarck's doctrine that variations spring from within the organism through its reaction to environmental conditions. 'All animals undergo perpetual transformations which are in part produced by their exertions in consequence of their desires and aversions, of their pleasures and their pains, or of irritations, or of associations; and many of these acquired forms or propensities are transmitted to their posterity.' 'Thus it would appear that all nature exists in a state of perpetual improvement by laws impressed on the atoms of matter by the great Cause of Causes; and that the world may still be in its infancy, and continue to improve forever and ever.'

"While Cuvier was extending and synthesizing the knowledge of anatomy of living and extinct forms and founding the so-called school of facts, his fellow countryman, Lamarck (1744–1829), on the basis of work first on plants and then on animals, carried on in a fearless manner the evolutionary inspiration of Buffon and Erasmus Darwin (though the latter's works may not have been known to him), and established the coterie of evolutionists in Paris each of whose essays Cuvier hailed as a 'new folly.' Lamarck developed with great care the first complete and logical theory of organic evolution, and is the one outstanding figure in biological uniformitarian thought between Aristotle and Charles Darwin. 'For nature,' he writes, 'time is nothing. It is never a difficulty, she always has it at her disposal; and it is for her the means by which she has accomplished the greatest as well as the least of her results. For all the evolution of the earth and of living beings, nature needs but three elements—space, time, and matter.'

"In regard to the factors of evolution, Lamarck emphasized the indirect action of the environment in case of animals, and the direct action in the case of plants. The former are induced to react and thus adapt themselves, while the latter, without a nervous system, are molded directly by their surroundings. And, so Lamarck believed, such bodily modifications—acquired characters—are transmitted to the next generation and bring about the evolution of organisms. . . .

"And then appeared the greatest work of Charles Darwin (1809–1882) the result of twenty years' labor. The *Origin of Species* (1859) presented a huge amount of data which most reasonably could be explained by assuming the origin of existing species by descent with modifications from others, and also offered as the explanation of their origin the theory of 'natural selection, or the preservation of favored races in the struggle for life.' In Darwin's words: 'As many more individuals of each species are born than can possibly survive, and as, consequently, there is frequently recurring struggle for existence, it follows that any being, if it vary however slightly in any manner

profitable to itself, under the complex and sometimes varying conditions of life, will have a better chance of surviving, and thus be naturally selected. From the strong principle of inheritance any selected variety will tend to propagate its new and modified form.'

"Facts and theories had been brought forward before in support of evolution—indeed, the theory of natural selection had been suggested before Darwin's time and again independently by Wallace (1822–1913) just as Darwin was completing his long studies preparatory to publication. But the stupendous task of thinking evolution through for the endless realm of living nature remained to be done, and Darwin did it convincingly by his brilliant, scholarly, open-minded, and cautious marshaling and interpreting of data.

"It was the combination of the facts and the theory to account for the facts which won the thinking world to organic evolution and 'made the old idea current intellectual coin.' Darwin supplied the Ariadne thread which led from the maze of transcendental affinity to genetic continuity. Now we know that evolution is a bird's-eye view of the results of heredity since the origin of life and that the facts of inheritance hold the key to the factors of evolution.

"Darwin spent the twenty years subsequent to the publication of the *Origin of Species*, as he had spent the preceding twenty years, in study and research, the results of which appeared in nine additional volumes. Three of these perhaps may be singled out as primarily an elaboration of the *Origin: The Variation of Animals and Plants under Domestication* (1868), *The Descent of Man* (1871), and *The Expression of the Emotions* (1872). Singly and collectively these volumes are a monument to genius and labor. Erasmus Darwin was wont to say that the world is not governed by brilliancy but by energy. His grandson revolutionized biological thought through their combination.

"Among Darwin's early converts from the ranks of professional biologists must be mentioned Huxley (1825–1895) and Hooker (1817–1911) in England, Haeckel (1834–1919) and Weismann in Germany, and Gray (1810–1888) in America—men with the courage of their convictions when courage was necessary, whose support did so much for the promulgation of evolutionary ideas. . . .

"Today no representative biologist questions the fact of evolution—'evolution knows only one heresy, the denial of continuity'—though in regard to the factors there is much difference of opinion. It may well be that we shall have reason to depart widely from Darwin's interpretation of the effective principles at work in the origin of species, but withal this will have little influence on his position in the history of biology. The great value which he placed upon facts was exceeded only by his demonstration that this value is due to their power of guiding the mind to a further discovery of principles.' Darwin brought biology into line with the other inductive sciences, recast practically all of its problems, and instituted new ones."

(Woodruff, "The Development of the Sciences," Chap. VI, pp. 251–259, Yale University Press, New Haven, 1923.)

Osmosis. See Diffusion.

Oxidation. "In recent years the important discovery has been made that oxidation processes yield energy because they are chemical reactions in which electrons shift from a position of high potential energy to one of lower, and in the shift set energy free. Modern physics has revealed that electrons possess much inherent energy; they tend strongly to exert force on one another. Each individual electron of an atom is subject to stresses and strains arising from all the other electrons, and the atom as a whole is thus the seat of a whole series of delicately balanced electron stresses. When atoms or molecules come into contact with other atoms or molecules the stresses are necessarily rearranged as the two sets of electrons exert their inherent forces on each other. It may happen that in the course of this rearrangement stresses will develop leading directly to electron shifts of the sort indicated, in other words to oxidation processes. Whether such electron shifts will occur depends primarily on what kinds of atoms or molecules come into contact. Thus oxygen has an electronic organization which fits it particularly to enter into reactions in which its atoms take up electrons. This special fitness, together with the very great abundance in which oxygen occurs in nature, explains why oxygen is one of the constituents in a great majority of oxidation reactions. The name *oxidation* derives from an early period of chemistry, long before the existence of electrons was known or even suspected, and before it was realized that the oxidations with which everyone is familiar are not the only reactions of the type but only the most common examples.

"Oxygen and other substances which, like it, can take up electrons under proper conditions, are known in modern chemistry as *oxidants*. Substances which tend under suitable rearrangements of electron stresses to transfer electrons to oxidants with liberation of energy are known as *reductants*. All substances commonly called *fuels* belong in this latter class." (Martin, "The Human Body," pp. 23–25, Henry Holt & Company, New York, 1935.) See Matter.

Paramecium. "The ciliated Protozoa, constituting the class Infusoria, probably represent the most complex development of the unicellular plan of animal structure. Infusoria have afforded ready material for the study of various physiological problems, not only because some of the species are relatively large, but also because, in general, they lend themselves readily to experiment. Most of the Infusoria are free-living in fresh and salt water, though not a few are parasitic. There is a highly complex fauna in the digestive tract of sheep and cattle, and man is not immune.

"The organization of the group may be illustrated by Paramecium which is a giant among the Protozoa, being just visible to the naked eye as a whitish speck if the water in which it is swimming is properly illuminated. When magnified several hundred times it appears as a more or less slipper-shaped organism which one would not consider, at first glance, a single cell because it shows highly specialized parts.

"The nuclear material in Paramecium, instead of forming a single body as it does in most cells, is distributed in two parts: a large MACRONUCLEUS, and one or more small MICRONUCLEI. Strictly speaking, the macronucleus and micronuclei together constitute the nucleus of the cell, and represent a sort of physiological division of labor of the chromatic complex which is characteristic of the Infusoria.

"But it is in the cytoplasm that specialization is most conspicuous. Not only are there general differentiations into ectoplasm and endoplasm, but these regions also have local specializations such as thousands of hair-like, vibratile CILIA for locomotion and securing food, TRICHOCYSTS for defense, PERISTOME, MOUTH, and GULLET for the intake of solid food, GASTRIC VACUOLES for digestion, and CONTRACTILE VACUOLES for excretion. And withal, recent investigations indicate that various parts of the cell are coördinated by a NEUROMOTOR SYSTEM.

"Paramecium, under normal conditions, grows rapidly and, when it has attained the size limit characteristic of the species, cell division takes place—a process of reproduction that can continue indefinitely if the environment is favorable. But periodically Paramecium undergoes an internal nuclear reorganization process (ENDOMIXIS). Also now and then individuals temporarily fuse in pairs and interchange nuclear material (CONJUGATION)—an expression of fundamental sex phenomena, involving fertilization.

"Indeed the Infusoria seem, so to speak, to have made the most of their unicellular plan of structure, for Paramecium is fairly representative: it is not the most simple nor yet the most complex. Specialization of one part and another of the cell has produced in the Infusoria a group of animals that, judged by distribution and numbers, is highly successful in the microscopic world of life." (Woodruff, "Foundations of Biology," pp. 473, 475–476, The Macmillan Company, New York, 1936.)

Pericardium. The mesodermal covering tissue that forms the thin, transparent pericardial sac in which the heart lies. See Serous Membranes.

Peritoneum. The mesodermal lining tissues of the abdominal or peritoneal cavity that are reflected as a covering over the various enclosed organs. See Serous Membranes.

Peritonitis. An infection of the peritoneum that lines the abdominal cavity. For example, a ruptured appendix will release infective agents into the body cavity which attack the peritoneum and cause peritonitis.

pH. See Hydrogen Ion.

Physiology, Development of. "Animal and plant physiology were discussed by Aristotle, but as might be expected, since physiology is more dependent than anatomy upon progress in other branches of science, with less happy results. Similarly, Galen was hampered in his attempt to make physiology a distinct department of learning based on a thorough study of anatomy, and the corner-stone of medicine. Like Aristotle he attempted to develop a picture of the *modus operandi* of the organism, and with such success that fate foisted it upon uncritical generations through fifteen centuries. And the unfortunate fact was not that Galen's physiology and anatomy were largely

incorrect, but that to question his authority was little less than sacrilege until the labors of Vesalius and Harvey brought a realization that Galen had not quite finished the work.

"Neither Vesalius nor Harvey made an attempt to explain the workings of the body by appeal to so-called physical and chemical laws; and for good reason. Chemistry had not yet thrown off the shackles of alchemy and taken its legitimate place among the elect sciences, while during Harvey's lifetime, under the influence of Galileo, the new physics arose. But by the end of the seventeenth century both physics and chemistry, aided by the philosophical systems of Bacon and Descartes, had forced their way into physiology and split it into two schools: the iatro-mechanical founded by Borelli (1608–1679), who by incisive physical methods attacked a long series of problems, frequently with brilliant results; and the iatro-chemical school, which developed from the influence of Franciscus Sylvius (1614–1672) as a teacher rather than as an investigator.

"This awakening brought a host of workers into the field and the harvest of the century was garnered and enriched by Haller (1708–1777), the 'abyss of learning' of the time, in a comprehensive treatise which at once indicated the erudition and critical judgment of its author and established physiology as a distinct and important branch of biological science, rather than as a mere adjunct of medicine. Great as was this contribution of Haller in crystallizing physiology and setting the dividing line between the old and the modern, unfortunately the weight of the author's authority was ranged in favor of two theories which were in crude form, attracting the attention of biologists—the idea of special vital force and the preformation theory of development.

"Perhaps the most significant lines of advance in Haller's century were in setting the physiology of nutrition and respiration—both of which waited upon the work of the chemists—well upon their way towards modern form. . . .

"Most of the foundation on which the physiology of animals rests today has been built up by works on vertebrates, though since the middle of the nineteenth century, when the versatile Müller showed the value of studying the physiology of higher and lower animals alike, the science of comparative physiology may be said to have been established. Perhaps it is not an exaggeration to say that the tendency to focus evidence, in so far as possible, from all forms of life on general problems of function represents the present trend of physiological inquiry.

"The less obvious structural and functional differentiation of plants retarded progress in plant physiology as it did in plant anatomy. Probably of most historical, and certainly of most general interest is the development of our knowledge of the nutrition of green plants.

"Aristotle's theory that the food of plants is prepared for them in the ground was still prevalent at the end of the sixteenth century when Cesalpino, the most philosophic botanist of his day, thought that food enters and passes through vessels and fibers of plants much as oil in a lamp wick, and Jung conceded that plants are not mere passive absorbers of ready-made food,

but possess the power of selecting from the soil the ingredients needed. But it was van Helmont, on the border line between alchemist and chemist, who precociously brought to bear the chemical point of view on animal nutrition. He planted a small tree in a large vessel and weighed it. Then after five years, during which time it had only been supplied with water, he found that it had increased some thirty-fold in weight and 'not suspecting that the plant drew a great part of its materials from the air was forced to exaggerate the virtues of rain-water.' Malpighi, however, from his studies on plant histology, gave the first hint of the fact of supreme importance that the crude sap, which enters by the roots, is carried to the leaves where, by the action of sunlight, evaporation, and some sort of a fermentation, it is 'digested' and then distributed as food to the plant as a whole. But it is Hales (1677–1761) to whom the botanist looks as the Harvey of plant physiology, for in his *Vegetable Staticks*, published in 1727, he laid the foundations of the physiology of plants by making 'plants speak for themselves through his incisive experiments.' For the first time it became clear that green plants derive an important element of their food from the atmosphere, and also that the leaves play an active role in the movements of fluids up the stem and in eliminating superfluous water through evaporation.

"Still the picture was incomplete, and so it remained until the biologist had recourse to further data from the chemist. In 1779 Priestley, the discoverer of oxygen, showed that this gas under certain conditions is liberated by plants. This fact was seized upon by Ingen-Housz (1730–1799), who demonstrated that carbon dioxide from the air is broken down in the leaf during exposure to sunlight; the plant retaining the carbon and returning oxygen—the process of carbon getting being quite distinct from that of respiration in which carbon dioxide is eliminated. It remained then for de Saussure to show, by quantitative studies of the plant's income, that, in addition to the fixation of carbon, the elements of water are also employed, while from the soil various salts, including the element nitrogen, are obtained. But it was nearly the middle of the last century before the influence of Liebig (1803–1873), and the crucial experiments of Boussingault (1802–1887) established the part played by the chlorophyll of the green leaf in making certain chemical elements available to animals. The realization of the cosmical function of green plants—the link they supply in the circulation of the elements in nature—is a landmark in biological progress, and we may leave the subject here since, except for details in regard to some of the more evident chemical products of photosynthesis and the influence of external factors, the matter still stands essentially where it was in de Saussure's day." (Woodruff, "The Development of the Sciences," Chap. VI, pp. 236–242, Yale University Press, New Haven, Conn., 1923.)

Pituitary—Historical. "The existence of the pituitary was known as early as the time of Galen (200 A.D.). The name *pituitary*, assigned to it by Vesalius, perpetuates an erroneous theory of its function that was long held. This designation ascribes to the gland the lowly office of secreting a fluid to lubricate the throat (Latin: *pituita*, mucus). The secretion was supposed to be

poured by minute channels into the nose cavity. This misapprehension was fostered by the porous nature of the bone that intervenes between the pituitary and the nasal cavity (cribriform plate of the ethmoid bone). Actually, there exist no such passages as the ancients surmised. The idea of the mucus-secreting function was overthrown by Conrad Schneider in a treatise on the membranes of the nose as early as 1660. No other function for the gland being known, it came ultimately to be regarded as merely a vestigial relic that had no particular importance to its possessor.

"One of the important functions of the pituitary is the promotion of growth. Accordingly, we find the earliest beginnings of our knowledge going back into primitive legendary lore. Giants have been known from time immemorial. Many peoples have held the belief that humanity has descended from races of enormous height. Curiously, the legend carried over into relatively modern times through misinterpretation of fossil remains. Actually, the giants of the neomythology were such huge creatures as the dinosaurs. A picturesque version of the belief is reported in the book of Deuteronomy. 'For only Og king of Bashan remained of the remnant of giants; behold his bedstead was a bedstead of iron; nine cubits was the length thereof, and four cubits the breadth of it, after the cubit of a man.' This description implies that the king was about 11 ft. in height. Goliath of Gath is another gigantic figure of popular lore. Pliny mentioned by name an Arabian giant 9½ ft. tall and reported, from hearsay, two others who had reached 10 ft. This gradual attenuation brings us to a scientifically verified case, that of Kayanus, a Finn, who was authentically nine and two-tenths feet tall.

"Actually, our knowledge of the involvement of the pituitary in bodily overgrowth was first appreciated in connection with a modified type of gigantism known as *acromegaly*. This condition had been recognized as a growth anomaly by Verga in 1864, and he made the further important observation that the pituitary gland in the patient he studied was abnormal. The eminent pathologist, Professor Klebs, thirty years later, wrote an excellent monographic study of a case of acromegaly. Klebs emphasized the fact that the pituitary gland was excessively large, but he was unable to decide whether this abnormality was the cause of or merely a part of the patient's general overgrowth. To the French neurologist Pierre Marie is usually given the credit for finally determining the relationship of the pituitary to the disease. His studies were reported in 1886." (Hoskins, "The Tides of Life," pp. 118–120, W. W. Norton & Company, Inc., New York, 1933.)

Plasmodium. "There are several recognized types of malaria parasites, all of which belong to the genus *Plasmodium*. The life cycle of this important organism involves a SEXUAL PHASE which must occur in the mosquito and ASEXUAL PHASES which occur in man and mosquito. The essential features of the life history may be outlined as follows: Man is infected by the bite of a female Anopheles mosquito which harbors the parasite in its salivary glands. The parasites when received into the blood stream are motile SPOROZOITES which are able to pass through the cell wall of the red blood corpuscles and into the cytoplasm where they remain as intracellular parasites and absorb

the life substance of the red cells as food. They increase in size until each sporozoite occupies almost the entire corpuscle. They then divide to form a great number of active MEROZOITES which burst the wall of the blood corpuscles and escape free into the blood stream where each attacks a new corpuscle.

"This asexual cycle in man occurs very rapidly and may be repeated indefinitely to produce a serious or even fatal case of malaria. Finally, sexual elements, the male and female GAMETOCYTES, appear in the blood corpuscles of the infected person and these must be transmitted to the mosquito for maturation. Accordingly if the victim is bitten once more by a mosquito the latter, in drawing the blood, will receive some of the gametocytes, which pass into the stomach and soon form free-swimming sperm and non-motile eggs. Fertilization occurs, and the newly formed zygotes, tiny active individuals, penetrate into the epithelial cells lining the stomach where each becomes an OÖCYST. A great increase in size occurs followed by asexual reproduction, or SPOROGONY, which results in the production within four or five days of numerous sporozoites. Breaking out of the oöcyst wall into the body cavity of the mosquito, they soon find their way to the salivary glands from where they pass into the human victim. Inasmuch as spore formation in the body of the mosquito is obligatory in the life cycle of the parasite, it is apparent that an infected person does not transmit malaria to others except indirectly by way of the mosquito.

"A rather close relative of the malaria parasite is the sporozoön, *Babesia*, which has a wide distribution and formerly caused great losses among domestic animals. In the United States it is the cause of a very serious disease in cattle, Texas fever. To the biologist the determination of the life cycle of this organism represents a landmark in achievement because it was the first protozoan disease known to be transmitted by an arthropod, in this case a tick. The results led to the development of successful methods of control and laid the foundation for many advances against disease-carrying organisms." (Baitsell, "Manual of Biology," pp. 80–82, The Macmillan Company, New York, 1936.)

Pleura. The mesodermal lining tissue of the thoracic cavity that is reflected as a covering over the lungs. See Serous Membranes.

Pneumonia, Determination of the Type. It has been established that there are three serological types of pneumonia which may be determined by agglutination tests. Horse serum, in which an agglutination has been developed by previous injections of a particular type of pneumococcus, is used in the typing. To carry out the test, it is necessary to secure an abundant supply of the pneumococci from the patient. This is quickly accomplished by securing sputum, emulsifying with salt solution, and injecting into the abdominal cavity of white mice. These animals are very susceptible to all types of pneumococci. In the abdominal cavity of the mouse, the bacteria grow very rapidly, and 24 hours later the peritoneal fluid will contain great quantities of pneumococci, which may be concentrated by centrifuging and then tested with each of the three types of horse serum, noted above, for the

agglutinating reaction. If the agglutinating reaction does not occur with any of the three types of serum, then the infection is due to Type IV pneumococci (Fig. 255).

Proteins. "These are the most important and most characteristic components of living matter. No living matter is known that does not contain them. They differ from the carbohydrates, fats, and lipoids in the facts that the molecules of most of them are much larger and more complex in their arrangement and that nitrogen forms a constituent part of the molecule. The average percentage composition of proteins is as follows:

	Per Cent
Carbon	50 to 55
Hydrogen	6.5 to 7.3
Nitrogen	15 to 17.6
Oxygen	19 to 24
Sulphur	0.3 to 2.4

"Other elements, for example, phosphorus, may be included in small amounts.

"The size of the protein molecule is always very large, since it is built up by the linkage of a number of relatively simple substances known as *amino acids.* Some 22 different amino acids are now known, and, as these are combined in varying numbers, proportions, and relations to each other, it will be apparent that the possible number of combinations that may be formed is almost beyond calculation. The various amino acids are linked in the protein by the joining of the COOH group of one to an NH_2 group of another, with the elimination of water, thus CO[OH H]HN. Some COOH and NH_2 groups are left uncombined.

"Proteins, because they contain both basic (NH_2) and acid (COOH) groups, are considered amphoteric electrolytes, capable of forming ionizable salts with acids as well as with alkalies, according to the hydrogen-ion concentration of the solution in which they are placed. They exist, therefore, in three conditions:

"1. They form salts with acids, as gelatin chloride. This occurs when the hydrogen-ion concentration exceeds a certain critical value, in this case pH 4.7.

"2. They form salts with bases, as sodium gelatinate. This action takes place when the hydrogen-ion concentration is below the critical value.

"3. At the critical value of the hydrogen-ion concentration, the protein is not able to combine with either an acid, a base, or a neutral salt. This critical hydrogen-ion concentration is called the *isoelectric point* of the protein.

"Among the chemical properties of the proteins of importance to the physiologist should be mentioned their general color reactions. These color reactions are due to a reaction between some one or more of the constituent groups of the complex protein molecule and the chemical reagent used in the particular test. Inasmuch as not all proteins contain all of the same groups, it is found that the tests vary in intensity of reaction. In case of any doubt it

is always wise to submit the sample under examination to more than one of the recognized tests before making a decision as to the nature of the substance." (Rogers, "Textbook of Comparative Physiology," pp. 33–34, 36–37, McGraw-Hill Book Company, Inc., New York, 1938.)

Protoplasm. The material substance in which life phenomena are exhibited. It is characterized structurally by its division into microscopic cells, which are the primary structural and functional units of living organisms. The term was first used in 1839 by Purkinje, a Bohemian biologist, to designate the vital substance that he found in various animal and plant materials. It was not, however, until 1861, from the researches of Max Schultze, that the concept of protoplasm as the universal life stuff of both plants and animals became firmly established. The cell is an organized mass of protoplasm typically differentiated into cytoplasm and nucleus and enclosed by a secreted nonliving cell wall; the thicker cell walls of plant cells consisting of cellulose, whereas those of animals are proteinaceous in nature. There are noteworthy differences between a so-called resting cell and one that is undergoing mitosis in that, in the latter, the nucleus disappears and the nuclear contents are united with the cytoplasm in the structural forms associated with mitosis. See Proteins; Biological Elements.

Protoplast. The protoplasmic mass in a cell exclusive of the nonliving cell wall. The term is most frequently employed by botanists in describing the contents of a plant cell enclosed within the heavy cellulose wall.

Protozoa. "The first great phylum is the Protozoa which comprises the most primitive forms of animal life, each individual being, as we know, a single unit of living matter. But it does not follow that the Protozoa are devoid of complex organization. Indeed some exhibit a complexity of structure within the confines of a cell that probably is not exceeded in the cells of higher animals. The Protozoa are the simplest, but by no means simple, animals, and their study forms the science of PROTOZOÖLOGY.

"All of the Protozoa, since they are single cells, demand for active life a more or less fluid medium, and are typically aquatic animals. However, different species exhibit all gradations of adaptation to variations in moisture from those that thrive in oceans and lakes, or pools and puddles, to those which find sufficient the dew on soil or grass blade, or the fluids within the tissues and cells of higher animals and plants.

"The phylum Protozoa is divided, largely on the basis of the locomotor organs, into four CLASSES: The Mastigophora, Sarcodina, Sporozoa, and Infusoria. In general, we may regard the MASTIGOPHORA as cells with flagella as locomotive organs, such as Euglena; the SARCODINA as forms, like Amoeba, that move about by means of pseudopodia; and the INFUSORIA as organisms, like Paramecium, that swim by cilia. The SPOROZOA, all of which are parasitic, such as the organisms causing malaria, possess no characteristic type of organ for locomotion though all are motile at some stage in their life history." (Woodruff, "Foundations of Biology," pp. 467–468, The Macmillan Company, New York, 1936.) See Metazoa.

Rabies Vaccine. The preparation of rabies vaccine begins with the securing of infected nerve tissue from the central nervous system of a rabid dog, containing the virus in its most active state. The inoculation of an individual with this material would be as dangerous as the bite of a mad dog. In order to reduce the virulence, the infected nerve tissue is emulsified and then injected into a rabbit where it develops slowly. Repeated transfers of the virus are made from one rabbit to another; altogether, a series of passages involving from 30 to 50 animals may be required. In time, the rabies virus becomes standardized as a "fixed virus" which will kill a rabbit 6 days after the infection. A final transfer of the fixed virus is then made. The rabbit receiving the fixed virus is not allowed to die from the infection but is anesthetized just before that time, and the infected spinal cord with the virulent fixed virus is removed from the body and sectioned, usually into 18 pieces. These spinal cord sections are now dried from 1 to 18 days to reduce the virulence of the virus so that it may be used for human vaccination. In sections dried for 1 day, the virus remains almost full strength but is progressively weakened by continued drying and is almost destroyed in sections dried for 18 days. Solutions are now made from each of the sections dried for the various periods, and these constitute the rabies vaccine. The treatment is begun with the vaccine made from the section dried for 18 days; and on successive days, increasingly stronger vaccines are given. Finally, at the conclusion of an 18-day period, the patient will receive an injection containing practically full-strength virus. But this is safe because, during the intervening days, the antibody formation has been incited, and the rabies virus in the vaccine as well as that injected by the bite of the mad dog will be destroyed before damage is done to the tissues of the central nervous system.

Secretagogues. "It seems that some foods contain substances designated as secretagogues, that are able to cause a secretion of gastric juice when taken into the stomach. Thus, meat extracts, meat juices, soups, etc., are particularly effective in this respect; milk and water cause less secretion. In other foods these ready-formed secretagogues are lacking. Certain common articles of food, such as bread and white of eggs, have no effect of this kind at all. If introduced into the stomach of a dog through a fistula so as not to arouse a psychical secretion—for instance, while the dog's attention is diverted or while he is sleeping—they cause no flow of gastric juice and are not digested. If such articles of food are eaten, however, they cause a psychical secretion, and when this has acted upon the foods some products of their digestion, in turn, become capable of arousing a further flow of gastric juice. The steps in the mechanism of secretion are, therefore, three: (1) The psychical secretion or appetite secretion; (2) the secretion from secretagogues contained in the food; (3) the secretion from secretagogues contained in the products of digestion. The manner in which the secretagogues act cannot be stated positively." (Howell, "A Textbook of Physiology," p. 824, Courtesy of W. B. Saunders Company, Philadelphia, 1937.)

Serous Membranes. "The Tissue of the Serous Membranes. The serous membranes (the *peritoneum*, the *pleura*, and the *pericardium*) are

thin layers of loose connective tissue covered on their free surfaces by a layer of mesothelium. When the membranes are folded, as the omentum or the mesentery, both of the free surfaces are covered with mesothelium. The serous cavities always contain a small amount of serous liquid, the *serous exudate.* The cells floating in it originate from the serous membrane.

"All the elements of the loose connective tissue are found in the serous membranes, where they are arranged in a thin layer. The mesentery contains a loose network of collagenous and elastic fibers, scattered fibroblasts, fixed macrophages, mast cells, and a varying number of fat cells along the blood vessels.

"Physiologically the most important, and histologically the most interesting part of the serous membranes in mammals is the omentum." (Maximow and Bloom, "A Textbook of Histology," p. 64, Courtesy of W. B. Saunders Company, Philadelphia, 1934.)

Sexual Characteristics (Secondary). "In the folk thought of all times, the testes have figured as the source of virility. Not only because of the resulting sterility but even more, perhaps, because of the effect upon the personality of the subject, emasculation has always been regarded as a major calamity. From time immemorial, removal of the testes, castration, has been practiced on boys and the common farm animals. The operation has been a religious rite among various sects, for example, until recently, the Skoptzs of Russia. The eunuch thus produced has had a special utility in various organizations of society, particularly as guardians of harems. As late as 1870, the operation was practiced to conserve the high-pitched singing voice of boys of a famous choir. It was from observations of individuals who had undergone such mutilation that the popular impression was derived. . . .

"Wheelon has defined sex as 'dependent upon the sum total of the somatic characteristics and differences associated with the reproductive tissue.' He continues: 'In addition to the evolution of male and female genital organs arose other phenomena by which the sexes are characterized. Such characters were designated by John Hunter as secondary sexual characteristics. This term embraces all those specific differences between the male and the female . . . which are not directly concerned with the processes of reproduction. Such characters are usually more elaborate in the male than in the female. Familiar examples of these characters are found in insects and vertebrates but are rare or absent in the lower invertebrates. The horns of the stag, the mane of the lion, the great variation of color among birds, the phosphorescent organs of the fire-fly, and the distribution of hair in man, are typical examples of secondary sexual characteristics.'

"In addition to the anatomical and physiological differences between males and females, distinctive sexual instincts have arisen also. In the higher forms, these include the impulses that bring the male and female together at the breeding season. They control the behavior of the individuals in their reciprocal relationships, such as courting and mating. Finally, they initiate the various activities involved in the building of the nest and the rearing of the young. In many animals, the sexual instincts are operative only during

the breeding season. The utility of this adaptation is obviously to insure that offspring will not be produced at unfavorable times of the year. Various of the secondary sex characteristics, too, are exaggerated during the breeding season only to wane with its passing. In many of the higher forms, the periodical changes in the secondary sex characteristics are directly under the control of the primary sex glands." (Hoskins, "The Tides of Life," pp. 170–173, W. W. Norton & Company, Inc., New York, 1933.)

Skin Glands. "The glands of the skin are of two kinds, the *sudoriparous* or *sweat-glands*, and the *sebaceous* or *oil-glands*. The former belong to the tubular, the latter to the racemose type. The *sweat-glands* lie in the subcutaneous tissue, where they form little globular masses composed of a coiled tube. From the coil a duct (sometimes double) leads to the surface, being usually spirally twisted as it passes through the epidermis. The secreting part of the gland consists of a connective-tissue tube, continuous with the dermis along the duct; within this is a basement membrane; and the final secretory lining consists of several layers of gland-cells. A close capillary network intertwines with the coils of the gland. Sweat-glands are found on all regions of the skin, but more closely set in some places, as the palms of the hand and on the brow, than elsewhere: there are altogether about two and a half millions of them opening on the surface of the body.

"The *sebaceous glands* nearly always open into hair-follicles, and are found wherever there are hairs. Each consists of a duct opening near the mouth of a hair-follicle and branching at its other end: the final branches lead into globular secreting sacules, which, like the ducts, are lined with epithelium. In the saccules the substance of the cells becomes charged with oil-drops, replacing all the protoplasm except the basal part where the nucleus is located; finally the whole outer part falls to pieces, its detritus constituting the secretion. This outer portion is then reformed, to provide material for further secretion. Usually two glands are connected with each hair-follicle, but there may be three or only one." (Martin, "The Human Body," pp. 592–593, Henry Holt & Company, New York, 1935.)

Smallpox Vaccine. In the preparation of smallpox vaccine by the great commercial biological laboratories, every precaution is taken to insure sterile cultures of smallpox virus that have been so treated as to reduce their virulence to a safe level. Several steps are involved which may be briefly summarized. In the first place, it is necessary to secure the virus either from cowpox material or from vaccination scabs. The latter are obtained from healthy children about 19 days after vaccination, at which time the scabs are well dried and about ready to slough off, but they still contain active virus of smallpox. The virus-containing material is then emulsified with a salt solution to form a vaccination paste. If this material were used for human vaccination, the virus would probably develop rapidly and give a severe case of smallpox to the recipient. Accordingly, methods have been devised to reduce its virulence. As the first step, the virus paste is inoculated into the sterile shaved skin on the abdomen of a calf. After the virus has developed here for a specified time, the human-bovine virus is collected from the inoculated areas, but it is

not yet suitable for human inoculation. The virus material is next diluted with sterile salt solution and used to vaccinate rabbits; the virus solution being rubbed into the skin from which the hair has just been shaved. In a few days the human-bovine-rabbit virus is collected and mixed in the proper proportions with a sterile water solution of glycerin, together with a minute amount of carbolic acid. At this stage, the material is known as *seed vaccine,* but it is still not used for human inoculation. For the final animal passage, young female calves, which have been under observation for some time in order to be sure of their freedom from disease, are taken. The hair is closely clipped from the flanks and abdominal regions, and these areas thoroughly washed until the skin is sterile. Now the seed vaccine is used to inoculate about 100 tiny areas in the prepared skin. In a few days, pustules containing human-bovine-rabbit-bovine smallpox virus will develop in each inoculated area. The calf is then killed and the smallpox vaccine collected under the most rigid aseptic conditions. After mixing with glycerin, the vaccine is allowed to stand for some time until exact tests have been made to determine its purity and strength.

These necessarily elaborate methods result in the production of smallpox vaccine that contains living smallpox virus of reduced virulence and suitable for human inoculation. Implanted in a minute area of the human skin, the smallpox vaccine produces a highly inflamed, but localized, reaction. The inflammatory reaction results in antibody formation that destroys the implanted virus and also renders the individual immune to smallpox for a considerable period.

Spontaneous Generation. See Biogenesis.

Staining. See Histology.

Starch. "The higher carbohydrates—the polysaccharides or nonsugars—are mostly insoluble in water, but they take up water readily and form pastes and jellies; they are therefore colloidal.

"The starches are sometimes referred to as *amyloses* and, together with the celluloses, as *hexosans,* because on hydrolysis they yield hexose sugars:

$$(C_6H_{10}O_5)_x + (H_2O)_x = xC_6H_{12}O_6$$

Starch is one of the most widely distributed of substances in the vegetable kingdom; it is the chief storage food of plants and may constitute 70 per cent of the dry weight of seed. The structure of the starch grain, as it occurs in the plant, is very characteristic and is used as a means of identification. Its chief distinguishing feature is its layered, or lamellar, structure. Starch is of biological importance because of its nutritive qualities, its extraordinarily high imbibition pressure, and its paste-forming qualities. Whether or not the imbibition pressure of starch is in part responsible, as has been maintained, for the carrying of water to the tops of trees cannot be said, but it certainly plays a part in bringing water into the cell. The gelatinous properties of starch may, to a great extent, be responsible for the highly viscous properties of protoplasm. Starch paste has some of the properties of a true elastic jelly and some of those of a plastic mass, but much of the viscous, glutinous,

and elastic properties that one might be inclined to attribute to starch, for example, in such substances as bread dough, are in great measure due to associated matter. Gluten comprises 10 per cent of wheat. When flour is freed of starch, gluten remains behind as a tenacious sticky mass. It is less abundant in foods than is starch but an equally valuable foodstuff.

Another amylose is dextrin; it is an intermediate product between starch and glucose. Some of the so-called "soluble" starches are probably dextrins. They are not abundant in plants. Dextrin is used as a substitute for gum.

Glycogen, or animal starch, occurs rarely in plants—in only a few of the fungi. It has risen to great prominence of late as the fuel for muscular action, though it has long been recognized as a substance of great physiological importance, especially in the liver where formerly it was thought to exist simply as stored excess carbohydrate but now is viewed dynamically, that is to say, as fuel for energy." (Seifriz, "Protoplasm," pp. 456–457, McGraw-Hill Book Company, Inc., New York, 1936.)

Sterols. The word *sterol* means solid alcohol. The sterols are widely distributed in nature. Because their solubilities are similar to those of fats, they were formerly classified as lipoids. But they are really alcohols and not chemically related to fats. Cholesterol, formerly called *cholesterin*, is the best known member of the group of sterols. Its formula, $C_{27}H_{45}OH$, shows one $-OH$ group indicative of an alcohol. It is related in its chemical structure to many substances of biological interest, including bile acids, certain hormones and vitamins. It resists chemical agents, save concentrated mineral acid or powerful oxidizing reagents. It is a very stable substance.

Cholesterol appears to occur in every animal cell, also in blood, lymph, and bile. It occurs abundantly in gallstones which are usually the result of crystallization of cholesterol from the bile. (Mitchell, "Textbook of General Physiology," p. 259, McGraw-Hill Book Company, Inc., New York, 1938.)

Suprarenals. See Adrenal Glands.

Sucrose (Cane Sugar). "Sucrose occurs commonly in the vegetable kingdom, being found in considerable quantity in many familiar fruits and vegetables. Usually these sweet fruits and plant juices contain glucose and fructose along with the sucrose, and also other substances which make it difficult to separate the sucrose in crystalline form. The juices of the sugar cane, the sugar beet, and to a less extent certain maple and palm trees, contain enough sucrose and little enough of other substances to make it practicable to manufacture sugar from them commercially. On hydrolysis a molecule of sucrose yields one molecule each of glucose and fructose. The process is often called 'inversion' and the product 'invert sugar.' When eaten, sucrose is digested into glucose and fructose. . . . (Sherman "Food Products," p. 9, The Macmillan Company, New York, 1926.)

Syphilis—Historical. "Few diseases mean more to the human race as a whole than syphilis, owing in part to its almost universal distribution and in part to its insidious and deceiving course, thereby leading to untold misery and disaster. Rosenau says 'civilization and syphilization have been close

companions'; the one has followed in the wake of the other like the guerillas behind an army. Unlike most diseases, syphilis is one of whose origin among civilized nations we have strong evidence. There are many reasons for believing that syphilis was acquired by the members of Columbus' crew when they discovered the island of Haiti and that it was carried back to Spain by them on their return. These adventurers promptly joined the army of Charles VIII of France in its invasion of Italy in 1494. Soon after the army had triumphantly set up a court in Naples, it became weakened through the ravages of a terrible venereal disease of unusual intensity, hitherto apparently unknown in Europe. The following year, the army retreated almost in a rout and was broken up, the miscellaneous troops scattering all over Europe to their respective home countries and carrying the new disease with them. In the next four years, the disease had spread to practically every country in Europe and was soon carried by the Portuguese to Africa and the Orient. The venereal nature of the disease was fully recognized, and its foreign origin was well known, each nation trying to shift the responsibility to another by name, many peoples calling it the 'French disease,' others the 'Spanish disease,' etc., whereas the Spanish alone seemed aware of its real origin in America and called it *española* which then meant Haiti. The absence of any reference to a disease resembling syphilis in the historical records before the discovery of America; the absence of any bones showing evidence of syphilitic attack in the abundant pre-Columbian remains in Europe, and abundance of such bones in American remains, many of which must certainly be pre-Columbian; the positive evidence of Spanish physicians and historians at the time of the return of Columbus; and the severity of the great epidemic in the latter part of the fifteenth century—it being almost invariable for an infectious disease, when first introduced among a new people, to rage with unwonted severity; all these facts point strongly to the American origin of syphilis.

"Interesting as is the early history of the disease, the recent history is infinitely more so. By the beginning of the twentieth century, medical men had come to the end of their rope in knowledge and treatment of the disease and found themselves at a standstill. But, in 1902, the disease was successfully transmitted to animals where it could be conveniently studied; in 1905, Schaudinn discovered the causative organism, *Treponema pallidum*, which is believed to cause the disease. In 1906, Wassermann demonstrated the possibility of detecting latent syphilis by the reaction that bears his name; in 1910, Ehrlich made the epoch-making discovery of his famous drug, 'No. 606,' or Salvarsan, a deadly poison for spirochetes of all kinds and a cure for syphilis in nearly all stages; in 1913, the direct relation of syphilis to insanity, paralysis, and other diseased conditions of the central nervous system was demonstrated by the discovery of the organisms in the cerebrospinal fluid; and in the same year, a method of destroying the parasites in the central nervous system was discovered. There is no other instance in the history of medical science where such wonderful strides have been made in such a short time in the knowledge and control of a disease. At the beginning of the twentieth

century, syphilis was one of the most horrible, hopeless, and tragic diseases known to ravage the human body; it is now a disease that can be readily recognized even in latent stages; it can be cured in its early stages; and the terrible tragedies resulting from apparent but imperfect cure can be avoided. Its eradication, however, will not soon, if ever, be accomplished, since in this are involved some of the most intricate moral and social questions with which we have to deal." (Chandler, "Animal Parasites and Human Disease," pp. 48–49, John Wiley & Sons, Inc., New York, 1926. Reprinted by permission.) See Complement Fixation.

Taxonomy. "Classification has as its object the bringing together of things which are alike and the separating of those which are unlike. It is 'discrimination, description, and illustration—the necessary census task which forms the groundwork on which great theories may be built up'—a problem of no mean proportions when a conservative estimate today shows upwards of a million species of animals and plants, leaving out of account the myriads of forms represented only by fossil remains. Naturally the earliest classifications were utilitarian, or more or less physiological: edible and harmful, useful and useless, fish of the sea and beasts of the earth. But as knowledge increased, emphasis was shifted to the anatomical criterion of specific differences and thenceforth classification became at once an important aspect of natural history—a central thread both practical and theoretical. Practical, in that it involved the arranging of living forms so that a working catalog was formed which required nice anatomical discrimination, and therefore the amassing of a large body of facts concerning animals and plants. Theoretical, because in the process botanists and zoologists were impressed, almost unconsciously at first, with the 'affinity' of various types of animals and of plants and so were led to problems of their origin.

"From Aristotle, who emphasized the grouping of organisms on the basis of structural similarities, we must pass over some seventeen centuries, in which the only work of interest was done by herbalists and encyclopaedists, to the time of Ray (1628–1705) of Cambridge. As a matter of fact, the Theophrastan classification of plants as trees, shrubs, and herbs persisted until the end of the seventeenth century. Previous to Ray the term 'species' was used somewhat indefinitely, and his chief contribution was to make the word more concrete by applying it solely to groups of similar individuals which exhibit constant characters from generation to generation. Covering, as Ray's labors did, the classification of both animals and plants, it is probably not an exaggeration to regard him as the seventeenth century precursor of the great Swedish taxonomist, Linnaeus, for whom he paved the way.

"Like many another genius, Linnaeus (1707–1778) was a product of his time and, perhaps, one of the very best examples of the fact that 'the most original people are frequently those who are able to borrow the most freely'—to see a great deal in what to others appears commonplace. Linnaeus was first and foremost a botanist. Garnering much of the best which the past had to offer in taxonomy, and bringing to bear on it his supreme talent for 'classifying, coördinating, and subordinating,' Linnaeus gave botanical students

at once a practical method of classification of flowering plants, based chiefly on the number and arrangement of the stamens. At the same time he insisted on brief descriptions and the scheme of giving each kind of organism a name composed of two words, in which the second word indicates the species and the first, the genus, a group of closely similar species. In short, to name an organism is to classify. Linnaeus' success with botanical taxonomy led him to extend the principles to animals and even to the so-called mineral kingdom, the latter showing at a glance his lack of appreciation of any genetic relationship between species.

"Indeed, the terms genus and species to Linnaeus expressed a transcendental affinity since he believed that species, genera, and even higher groups represented distinct, consecutive thoughts of the Creator. Accordingly, the ultimate goal of taxonomy was to determine the so-called *scala naturae.* This viewpoint is somewhat whimsically expressed by an old naturalist who, finding a beetle which did not seem to agree exactly with any species in his collection, solved the difficulty by crushing the unorthodox individual under his foot. Thus, Linnaeus crystallized two dogmas—constancy and continuity of species—which permeated biology and reached, in slightly different form, their high-water mark, indeed a *reductio ad absurdum,* in Agassiz's *Essay on Classification* a century later—as fate would have it, just a year before Darwin's Origin of Species appeared.

"Though today Linnaeus' conception of fixity has been replaced by modifiability of species, the affinity which he recognized and expressed in transcendental terms has given place to similarity based on descent, and his artificial classifications have been superseded by natural classifications, which express, or attempt to express, this genetic connection between species—nevertheless his greatest works, the *Systema Naturae* and *Species Plantarum,* created an epoch in biological history, and are by common consent the base line of priority in zoological and botanical nomenclature." (Woodruff, "The Development of the Sciences," Chap. VI. pp. 230–232, Yale University Press, New Haven, Conn., 1923.)

Thyroid—Historical. "The swelling of the thyroid gland, commonly known as *goiter*, has been familiar to physicians as well as laymen from time immemorial. Juvenal reflected this familiarity in the line *Quis tumidum gutter miratur in Alpibus*—'Who wonders at goiter in the Alps!' Beyond the existence of the glands, however, and their liability to goitrous swelling, the knowledge of the ancients did not go. During the centuries of antiquity, numerous theories engaged the imagination of thinking men, but no one descended to the unfashionable procedure of grubbing for facts. Some scholars regarded the thyroid as a protective device to keep the throat warm, 'to cherish the vocal cords.' Others ascribed the gland to the aesthetic impulse of the Creator who established it for the sole purpose of rounding out the neck in a beautiful contour. The theory that gained most favorable currency in the nineteenth century was that the thyroid, like the adrenals and the thymus, has no significance except during the stage of life that precedes birth.

"Professor Schiff of Geneva was the first to put this theory to the serious test of experiment. He removed the glands from a series of animals, following which death soon ensued. This fact he first communicated verbally to the Academy at Copenhagen, then later published—in 1858. But Schiff's observations made no impression on contemporary physiology. As Meltzer says, physiologists at that particular time had neither any great interest in pure biologic researches nor special confidence in their results. The fashion then was to try to explain all the phenomena of life in terms of inanimate machinery.

"For awakening practical interest in the functions of the thyroid, the world is indebted to clinicians rather than physiologists. In 1873, Sir William Gull, the surgeon, reported the cases of five middle-aged women whose puffy faces, bulky forms, and physical lethargy indicated the presence of a common disease. Five years later, Ord, another British physician, who had had similar patients under observation for ten years or more, performed a post-mortem examination on one of the victims. He noted that the thyroid gland was atrophic and that the general puffiness of the external layer of the body was due to the accumulation of mucilaginous material in the tissues under the skin. It was this characteristic that caused him to designate the new disease as *myxedema* (mucoid swelling).

"The next step in discovery came also from surgery. With the general introduction of antisepsis by Lister in the beginning of the 'seventies, surgeons were emboldened to carry operative technic into regions of the body up till then recognized by common consent as inaccessible. They now began to treat goiters by radical operation. Rederdin of Geneva reported on a few of these cases in 1883. The work received little notice, but, during the same year, Kocher of Bern gave a more extensive report that included a discussion of the after-effects of complete removal of the goitrous glands. He emphasized especially the marked interference with nutrition. In November of that same year, Semon called the attention of the Clinical Society of London to the similarity between the symptoms of myxedema and those following surgical removal of the thyroids. He suggested that the glands might be of fundamental importance to life.

"The topic by this time had become one of keen interest among members of the medical profession, and Professor Schiff was led to repeat and extend his earlier experiments. He found that, in dogs, complete removal of the thyroid was commonly followed by death and that the symptoms in various respects resembled those following complete removal of goitrous glands in man.

"A German, Bruns, then entered into the discussion. He had noted, in the literature, a report of a case of a boy from whom a goitrous thyroid had been perilously removed ten years before the advent of the antiseptic period. He sought out the subject and obtained confirmation of the growing conviction that the thyroid plays an important role in body metabolism. The lad had managed to survive the operation and was then nearly forty years old; but in size and appearance, he resembled a mentally and physically backward boy. In short, he presented the typical picture of myxedema.

"At the end of 1884, then, the new knowledge could have been summarized to this effect: Natural absence of the thyroid glands in adults causes the disease myxedema; in children, it results in arrested growth; complete removal of the normal thyroid in animals results in death; in children or in adults, complete removal of the glands is soon followed by surgical myxedema identical with that occurring spontaneously from thyroid deficiency. Clearly enough it was evident that the thyroid gland is of fundamental importance to the health—perhaps even the life—of man or animal.

"Schiff, the physiologist, immediately brought forward still stronger evidence in favor of this thesis. He found that if one of the lobes of the thyroid gland was transplanted into the body cavity of an animal, it could survive for a long time the removal of the other lobe—final proof that the disturbance following the thyroid operation was due to a lack of the gland tissue and not to general operative injury as such.

"In the years that followed, numerous experimental investigations were made that confirmed the main facts and added many new details. It is interesting that these physiologic investigations were mostly made, however, by surgeons rather than by professional physiologists whose special business it is to study such problems. Curiously, Munk, the only physiologist to enter the lists, is remembered now for his share in the work only because of the erroneous claim that he persistently supported, namely, that the results following removal of the thyroid were due merely to incompetent surgery that resulted in injury of the important nerves coursing near the glands.

"The disastrous effects of thyroid deficiency having become known, the next logical step in research was clearly enough seen. This was to attempt the treatment of naturally occurring thyroid deficiency by replacing the missing tissue. In 1889, the first case of successful thyroid grafting was reported. After implantation of living thyroid tissue, all symptoms disappeared for a considerable period, but ultimately the grafts were absorbed and the symptoms reappeared. It seemed then that the thyroid graft amounted in effect merely to the injection of thyroid material, and the next step was obviously to employ simple injections. These proved to be successful and might have continued to this day to be the treatment of choice for the symptoms of thyroid deficiency had it not soon been learned that the administration of gland substance by mouth is equally effective and much less troublesome. This fact was first reported by Fox in 1892.

"In one short decade, then, more was learned about the thyroid gland by the methods of biologic research than in all the centuries that had gone before when men were content simply with observations upon such patients as passed before their eyes." (Hoskins, "The Tides of Life," pp. 64-67, W. W. Norton & Company, Inc., New York, 1933.)

Tropism. "When a sessile animal or a fixed plant bends or grows in a definite direction in response to a definite stimulus, turning, for example, toward the sun, the movement is called a tropism. This term has been extended to include the definite oriented movements of motile organisms. If a plant or animal turns or moves toward the source of the stimulus, it is

said to show positive tropism; if it turns or moves away from the source of the stimulus, it is said to show negative tropism. Positive heliotropism or phototropism is the tendency to turn or move toward light. Positive galvanotropism is the tendency to turn or move toward the positive pole (anode) when in the stream of an electric current. Positive geotropism is the tendency of the roots of a plant or of parts of animals to grow or to bend downward under the influence of gravity. Similar upward growth or bending is negative geotropism. Positive chemotropism is the tendency of an organism to turn or move toward the source of a given chemical substance which is diffusing from its source into the surrounding medium. Stereotropism is the tendency of an organism to orient itself in a certain definite way with respect to solid bodies. Numerous other tropisms have been described, for example, rheotropism or orientation with respect to stream flow and thermotropism or orientation with respect to a source of radiating heat in the environment; but as many of these reactions can be shown to be due to other tropisms or to behavior which is not typical of a tropism, they will not be discussed here. The terms, phototaxis, chemotaxis, etc., are sometimes used with the same meanings as those of the corresponding tropisms.

"Tropisms afford an explanation for many aspects of animal behavior, which the physiology of reflexes alone cannot explain. In a certain sense, a tropism is itself a reflex when it occurs in an animal with a central nervous system, but differs from a reflex in that it involves the coordinated action of so many reflex arcs that it may be regarded as a reaction of the organism as a whole. A reflex, on the other hand, need not necessarily involve so many different reflex arcs as a tropism, so that only a segment or small portion of an animal responds." (Mitchell, "Textbook of General Physiology," pp. 128–129, McGraw-Hill Book Company, Inc., New York, 1938.)

Vaccines. See Rabies; Small pox.

Vertebrates in General. The animal kingdom is commonly said to be divided into the INVERTEBRATES and the VERTEBRATES. The basic distinction between these two groups may be said to be the presence in the latter of a dorsal supporting axis, the vertebral column, which is of paramount importance in its relations to the general supporting structures of the body and in the protection rendered to the delicate spinal cord of the nervous system. The Vertebrates, on the other hand, belong to one phylum, the CHORDATA. This phylum also includes, in addition to the important vertebrate division, a small number of types that, for the most part, are aberrant structurally but possess, nevertheless, certain basic features which seem to link all of them together. The distinctive chordate features may now be noted:

1. A dorsal supporting axis, the NOTOCHORD, is present either throughout life or during early development. The notochord is a rod-like structure which lies dorsal to the alimentary canal and typically extends the entire length of the animal, but it is subject to considerable variation in the different chordate groups.

2. A tubular CENTRAL NERVOUS SYSTEM, which lies dorsal to the notochord and alimentary canal, is present either during embryonic development or

throughout life. In the Invertebrates that possess a central nervous system, the nerve cord always lies ventral to the alimentary canal and is a solid cord, instead of a tube.

3. At some period in their life history, the Chordates typically possess paired lateral openings, GILL SLITS, which connect the cavity of the pharynx directly with the exterior. These openings, when functional, permit the water taken in through the mouth to pass over vascularized tissues, which are developed in or near the walls of the gill slits, and then to the exterior. In the aquatic Chordates, this is essential in respiration.

Four major divisions, or subphyla, of Chordata are recognized, the first three of which are interesting from the comparative standpoint, but otherwise unimportant. They are as follows:

A. ENTEROPNEUSTA. A small group of marine animals, usually worm-like in size and appearance, but which may show great variation. The best known representative of the Enteropneusta is *Dolichoglossus* which is fairly common. It lives along the shore embedded in the sand or mud and secures its food in much the same way as the earthworm, that is, by digesting the organic material from the debris that passes through the tubular alimentary canal. The systematists are far from agreement as to the taxonomic position of this group.

B. TUNICATA. This subphylum contains several rather abundant marine organisms commonly known as the *sea-squirts*, due to their habit of ejecting a stream of water when disturbed. The mature individual of this group shows a degenerate condition as compared with the larva but possesses many gill slits and associated organs that serve both for respiration and for the capture of food. The adult is enclosed by a peculiar tunic largely composed of cellulose. This is possibly the only example in the animal kingdom of this material which is so very abundant in plant tissues.

C. LEPTOCARDIA. Only one genus consisting of a few marine species are classified in this subphylum, but included among these is the important species *Branchiostoma lanceolatus*, more commonly known as *Amphioxus*, or the *lancelet*. The importance of Amphioxus from the zoological aspect lies in its possession throughout life of structural features that seem to link it with the true Vertebrates as well as with the Chordates. It is a small fish-like animal a few inches in length and is able to dart about quite rapidly when disturbed. The adult, however, usually lies vertically in a sand burrow with only the anterior end of the body projecting. Amphioxus lacks a definite head, jaws, and limbs.

D. VERTEBRATA. The Vertebrata, by far the most important subphylum of the Chordates, including all the familiar animal types such, for example, as the fishes, frogs, snakes, birds, rabbits, and Man. Certain important diagnostic features of this subphylum—in addition to the three fundamental chordate characteristics—may now be briefly noted:

1. As indicated by the term VERTEBRATE and noted above, all these forms possess a backbone, or vertebral column. This important supporting structure is composed, except in the most primitive vertebrates, of a considerable

number of bony segments, or VERTEBRAE, which develop in close relation to the unsegmented notochord of the embryo and usually supplant it in the adult. The backbone ends in a postanal projection, the TAIL.

2. Vertebrate animals possess an internal supporting skeleton, the ENDOSKELETON composed essentially of living matter, and forming the bones, tendons, cartilage, and the very abundant connective tissues. Vertebrates also have either a partial or complete EXOSKELETON composed essentially of nonliving matter.

3. The vertebrate appendages are restricted in number. There are never more than two pairs present, and in many cases there are less. Thus in certain reptiles, such as the snake, limbs are lacking. It appears that the five-fingered PENTADACTYL limb is to be considered as the basic vertebrate type. The entire series of vertebrate limbs is regarded as homologous, including those of the horse which have retained only one functional digit on each limb.

4. The vertebrate heart is ventral, and the blood has a new type of red cell. The color of these cells is due to the important respiratory compound, hemoglobin, which, in the invertebrates, is carried as a dissolved substance in the blood plasma, rather than in specific cells.

5. Reproduction is always sexual. There is also an absence of hermaphroditism in the Vertebrates. The abandonment of both asexual reproduction and hermaphroditism appears to have been a comparatively recent step in the history of animal development.

We may now note the animals included in the main divisions of the subphylum Vertebrata.

CYCLOSTOMATA. This is a small class but nevertheless contains a number of fish-like species which are noteworthy because of certain primitive characters that differ from those of other vertebrates. Thus (*a*) the notochord persists throughout life; (*b*) a cartilaginous endoskeleton develops, is functional, and never replaced by bone; (*c*) the circular mouth opening, with no jaws present, shows a superficial resemblance to that of Amphioxus; (*d*) dorsal and caudal fins are present, but paired fins are lacking.

ELASMOBRANCHII. This class includes a number of species, some of which occur in great abundance in most marine waters. The sharks, dogfish, and rays (skates) belong to the Elasmobranchs. They show considerable advance over the Cyclostomes. Thus (*a*) the notochord is segmented, only partially persistent, and cartilaginous vertebrae have arisen; (*b*) a well-developed lower jaw is present and possesses modified scales that serve as teeth; (*c*) two pairs of lateral fins are found.

The common Dogfish, *Squalus acanthias*, has been found very satisfactory for laboratory study in comparative anatomy as an important example of the lower Vertebrates. Among the Rays, the Torpedo is particularly noteworthy because of the amazing modification of certain muscles, lying in the head region, which permit them to accumulate charges of electrical energy sufficient to paralyze large animals.

PISCES. This is by far the largest and most important group of fish including some 15,000 species of the so-called bony fishes, among which are the perch, cod, trout, mackerel, and salmon. Again considerable advances in organization over both the Cyclostomes and Elasmobranchs are to be noted. In fact, the Pisces are often referred to as the true fishes. Of outstanding importance is the fact that, for the first time, bone is developed in the endoskeleton. In most species of this class, the skeleton is almost entirely ossified, although in a few the original cartilaginous skeleton is replaced in part only. As a rule, the notochord is entirely replaced by the segmented, bony vertebral column. The external openings of the gill slits are covered, on each side of the body, by a fold of tissue, the OPERCULUM.

AMPHIBIA. This vertebrate class includes tailed forms (salamanders, newts) and also tailless types (frogs, toads). The tailed Amphibia are for the most part aquatic, and the gills are functional throughout life in some cases. The frogs and toads are fish-like in the tadpole stage; then they metamorphose into air-breathing, adult individuals which are different from the tadpole, particularly in the absence of the tail and the presence of two pairs of pentadactyl limbs. With very few exceptions, the amphibian skin is smooth and shows no exoskeletal structures, such as the scales of fishes or of reptiles. Even more noteworthy are the pentadactyl limbs, which mark a wide advance over the fish fin, and the development of lungs.

REPTILIA. In this class, we find a group of vertebrate animals that are air-breathing at all stages in their life history. The embryonic gills never function. The skin is marked by a considerable development of exoskeletal structures, such as are shown in the bony plates of the turtle or the scaly snake skin. Undoubtedly, reptilian development reached its peak in prehistoric periods when the living representatives included the enormous land-living Dinosaurs and related types.

Three important orders of the Reptilia are recognized, namely:

1. The *Testudinata*, consisting of the turtles and tortoises;
2. The *Crocodilia*, which includes the alligators and crocodiles;
3. The *Squamata*, represented by snakes, chameleons, and lizards.

AVES. Since the Aves are the only animals that possess feathers, this one character serves to differentiate the birds from all other groups. The main portion of a feather develops in the dermis of the skin, and is covered externally by an epidermal layer. Birds possess two pairs of limbs, but the fore limbs are highly modified for flying. Even the most primitive fossil birds show this important development, and it persists throughout all species.

Another interesting and important features found in this class is the maintenance of a uniform body temperature (homothermal), a condition that elsewhere is found only in the mammalian group. In all other animals, the body temperature varies with the environment (poikilothermal). Attention should also be called to the fact that birds and mammals possess a four-

chambered heart. Although teeth can be demonstrated in certain fossil birds, they are lacking in present-day species. The birds represent an extremely homogeneous group, so much so that it is very difficult to find a sufficient number of differentiating structural characters to construct a satisfactory scheme of classification for the nearly 20,000 species that are known.

MAMMALIA. This most important vertebrate class is characterized by the development of hair in the skin. Abundant in many species, where it forms a heavy external covering, in certain other types hair may be considerably restricted or in an extreme case, such as in certain whales, be entirely lacking. Another mammalian characteristic is noted in the mammary glands which form a secretion for nourishing the young after birth. A constant body temperature is maintained by all Mammals.

Probably the greatest amount of external variation is to be found in the structure of the appendages. These may vary from two pairs of pentadactyl limbs, as in man, to the condition found in the whale, where the fore limbs are paddle-shaped structures, although maintaining the fundamental pentadactyl arrangement, and the hind limbs are entirely lacking. Or again a reduction of digits may occur, as in the horse, where only the third digit of each limb is functional. In fact, a very complete series of mammalian appendages can be arranged to show the ADAPTIVE RADIATION from a basic or generalized type to the highly specialized types in conformity to the chosen environmental conditions.

Again, the exoskeletal structures show great variation and are used in classifying this group. Thus we have Mammals with claws, or UNGUICULATA (dog); Mammals with hoofs, or UNGULATA (horse); Mammals with nails (monkey, ape, man). The teeth are also important in this connection.

In all Mammals, except a few of the most primitive species, the fertilized egg is retained in the body of the mother for early development. It is interesting to note that in the primitive mammalian types, large-yolked eggs are laid that are very similar to those of reptiles and birds.

The Mammalia are commonly divided into two subclasses, the *Prototheria* and the *Eutheria.* The former are the egg-laying mammals. There are only a few species known, notably, *Ornithorhyncus*, the Duckbill, and *Echidna*, the Spiny Anteater. There are two basic groups of Eutheria: the more primitive Marsupials and the Placentals. The first named are the so-called pouched mammals. The young are born in a very immature condition and are carried for a time by the mother in a special pouch, the marsupium, present on the ventral surface of the female body. This is also a very small mammalian group with the kangaroo and the opossum as typical examples. The Placentals are born in a comparatively high developed condition. This is due to the PLACENTA in the female which enables the embryo to be retained for a longer period of uterine growth. Great importance attaches to the placental group, and further attention may now be given to its classification. Considerable variation in the arrangement of the mammalian orders is found among the systematists. Present purposes may be served by indicating nine orders as follows:

Order 1. *Insectivora.* This order includes certain well known species, such as the mole, hedgehog, and shrew.

Order 2. *Edentata.* Examples of his class are noted in such distinctive species as the armadillo, anteater, and sloth.

Order 3. *Chiroptera.* The bats which constitute this order are characterized by a modification of the fore limbs which adapt them for flight.

Order 4. *Rodentia.* This is the largest mammalian order in the number of species included. Also the number of individuals and the extent of the geographical distribution of certain species are extraordinary, for example, the mouse and the rat. Rodents are characterized as the gnawing mammals. They possess one or two pairs of long incisor teeth particularly adapted for this purpose. Claws are present on the digits. The destructiveness, high fertility, and disease-carrying ability of certain species make them pests of the first rank. All things considered, the rat is probably the most destructive and dangerous animal with which we have to contend. Additional examples of rodents are found in the squirrel, rabbit, guinea pig, beaver, gopher, and porcupine.

Order 5. *Carnivora.* The Carnivores are typically characterized as the flesh-eating mammals and possess teeth adapted for tearing animal tissues. On the whole, they are fairly large, clawed animals with a heavy coat of fur which is frequently of considerable commercial value. The Carnivora are clearly divided into the terrestrial forms, a few important examples of which may be noted in the dog, wolf, cat, lion, tiger, bear, raccoon, mink, and into the aquatic types, such as the seal, sea-lion, and walrus.

Order 6. *Cetacea.* This is a rather small order of exclusively marine animals and includes the whale, porpoise, and dolphin. The largest living animal, the Sulphur-bottom Whale, may reach a length of nearly 100 ft. and a weight close to 300,000 lb.

Order 7. *Ungulata.* For ages Man has found some of his most important animal allies among the Ungulates, including such almost indispensable species as horses, cattle, sheep, hogs, and camels. These and other species have long since been domesticated to provide constant supplies of animal food, materials for clothing, and transportation. We can characterize the Ungulata as the hoofed mammals and divide them into the even-toed and odd-toed types. Thus the cow, pig, and camel may be given as examples of the even-toed Ungulates, while the horse, rhinoceros, and elephant are examples of the odd-toed. Among the outstanding structural features of economic importance are the character of the flesh of certain species which makes it desirable for human consumption; the character of the skin, particularly in cattle, which makes it suitable to tan for leather; and, finally, the mammary glands of a few species which provide a supply of milk for human nutrition.

Order 8. *Sirenia.* A small, relatively unimportant order of aquatic Mammals, including the Manatee and Dugong, which appears to be closely related to the Ungulates.

Order 9. *Primates.* This final order of Mammals, which includes Man, is primarily characterized by the great development of the brain; a feature

generally regarded as being of sufficient importance to make it necessary to place this group as the highest order of the Mammals, even though in various other features, such as the development of the muscular tissue, character of teeth, and condition of young at birth, the Primates are less advanced than certain other orders, particularly the Ungulates. Other characteristics are noted in the digits, which bear nails rather than claws or hoofs, and also in that the first digits (toe or thumb) are opposable (one or both) to the other digits. The primate appendages are primarily adapted for grasping, a function that corresponds to the arboreal habitat of the great majority of species.

The Primates may be divided into two suborders on the basis of a comparatively minor structural feature, namely, the separation or contact of the front teeth in the anterior median line. Thus in the suborder *Lemuroidea* the teeth are separated, while in the suborder *Anthropoidea* the teeth are in contact.

The *Anthropoidea* includes the tailed monkeys, with numerous species in South America and various regions in the Old World, and the short-tailed anthropoid Apes, represented by the gibbon, orang-utan, chimpanzee, and the rare gorilla. Man is classified as a separate family (*Hominidae*) of the *Anthropoidea.* Only one species, *Homo sapiens*, is recognized at present. The anthropoid Apes are regarded as the closest structurally to Man. This is based on such features as the absence of a tail, the frequent occurrence of bipedal locomotion, the very high degree of intelligence, and the almost human facial structure and expression due to the enlarged cranial bones and reduced facial bones.

In Man, the bipedal locomotion is universal, the big toes are not opposable to the other digits, the formation of hair is not so abundant, and, above all, the tremendous development in the size and quality of the forebrain has given a mental superiority that far transcends that of any other living organism. The superior mental equipment of Man has enabled him to dominate other types of living organisms and to surmount highly diverse climatic conditions so that his distribution is world-wide. (Baitsell, "Manual of Biology," selected from pp. 253–267, The Macmillan Company, New York, 1936.)

Viscosity. "Viscosity may be roughly defined as the resistance of matter in the liquid or semiliquid state to change in shape. It is usually measured by the time required for the passage of a standard volume of the liquid through a narrow-bore tube under standard conditions of temperature and pressure. Viscosity is really the internal friction of a liquid, its resistance to flowing or to shearing stresses. It may thus involve not only the mutual attraction, cohesion, of molecules but also their tendency to maintain a certain arrangement or "pattern," that is, their tendency to orient themselves with respect to one another.

"Although the usual type of viscosimeter is a narrow tube, other forms are in use. One of them measures the torsion of a wire that suspends a cylinder immersed in the liquid to be measured while the latter is kept rotating at constant speed. The viscosity of the liquid causes friction as it rotates around the cylinder so as to drag it along. The resulting torsion in the suspending

wire, observed in angular degrees, can be converted by the use of an equation into viscosity units." (Mitchell, "Textbook of General Physiology," pp. 392–393, McGraw-Hill Book Company, Inc., New York, 1938.)

Volvox. Colony formation is widespread among the flagellated organisms. This phenomenon reaches its climax in the beautiful fresh-water form Volvox, the spherical body of which consists of several thousand attached cells, very similar to those in various unicellular flagellates in their structural features. By the botanist, Volvox is classified as the highest of the colonial Green Algae, whereas the zoologists generally place it among the Mastigophora and regard it as the most plant-like of the colonial Phytomastigina. Our interest in Volvox lies in the fact that it represents a primitive type of multicellular organism in which the constituent cells have become somewhat dependent upon each other and which also exhibits a certain amount of intercellular differentiation in that specialized reproductive cells, which are unlike the normal body cells, are developed in the mature colonies. Thus Volvox may be said to represent the beginnings of the true multicellular organism with slight indications of the cellular dependence and specialization so prominently shown in all the higher plant or animal forms.

In the true multicellular plants and animals, Metaphyta and Metazoa, all of which in an early stage are essentially colonies of undifferentiated cells, more and more intercellular specialization takes place as the organisms gradually attain maturity. This process, of course, results in a division of labor between the cells, so that, in the mature organism, the various cellular groups do not perform all the functions essential to the life of the organism but only the particular functions for which they are structurally adapted.

Volvox is large enough to be seen with the naked eye. It appears as a small, green, hollow sphere, the wall of which is composed of some 10 or 12 thousand microscopic, flagellated, chlorophyll-bearing cells, arranged in a single layer and surrounded by a transparent, gelatinous, intercellular material, the MATRIX. The latter is formed as a cellular secretion and serves apparently to hold the cells of the colony together. (Baitsell, "Manual of Biology," pp. 63–64, The Macmillan Company, New York, 1936.)

Wassermann Test. See Complement-Fixation.

Water. See Dissociation.

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